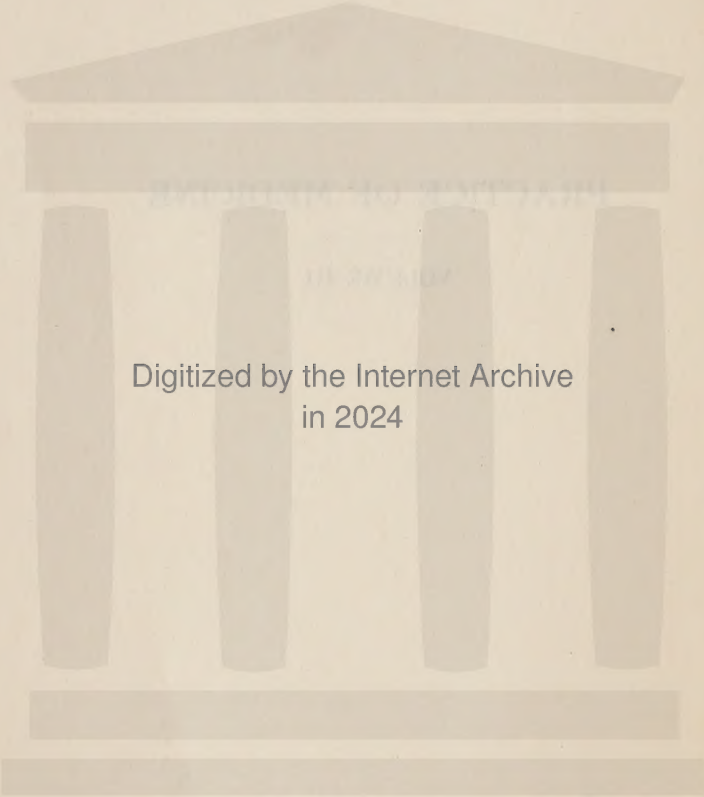


PRACTICE OF MEDICINE

VOLUME III

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PRACTICE OF MEDICINE

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VOLUME III

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PRACTICE OF MEDICINE

FRANKLIN J. FINE, M.D.

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CONTENTS

VOLUME III

SECTION II: INFECTIOUS DISEASES (*Continued*)

CHAPTER	PAGE
V. ACUTE LOBAR PNEUMONIA	1
By CHARLES R. AUSTRIAN	
VI. CEREBROSPINAL FEVER	83
By J. P. LEAKE	
VII. DIPHTHERIA	131
By ROBERT A. STRONG	
VIII. ERYSIPELAS	177
By H. B. CUSHING	
IX. VARIOLA (SMALLPOX)	187
By SAMUEL SIDNEY WOODY	
X. VACCINIA (VACCINATION)	215
By SAMUEL SIDNEY WOODY	
XI. VARICELLA (CHICKENPOX)	223
By SAMUEL SIDNEY WOODY	
XII. SCARLET FEVER	233
By SAMUEL SIDNEY WOODY	
XIII. RUBEOLA (MEASLES)	281
By WILLIAM A. JENKINS	
XIV. RUBELLA (GERMAN MEASLES)	301
By WILLIAM A. JENKINS	
XV. PAROTITIS EPIDEMICA (MUMPS)	311
By WILLIAM A. JENKINS	
XVI. SYPHILIS	329
By JOHN H. STOKES	
XVII. GONOCOCCAL INFECTIONS	451
By DAVID GEIRINGER AND JORGE CAMPUZANO	

CONTENTS

XVIII	RABIES	521
	By <i>EDGEE R. WHITMORE</i>	
XIX	MALARIA	531
	By <i>CHARLES C. BABB</i>	
XX	SAND FLY FEVER	615
	By <i>EDGAR EBERHART HUMM</i>	
XXI	TULAREMIA	665
	By <i>EDWARD FRANCIS</i>	
XXII	PESTITIS	679
	By <i>JAMES B. LUCKIE</i>	

LIST OF ILLUSTRATIONS

VOLUME III

SECTION II. INFECTIOUS DISEASES (*Continued*)

CHAPTER XVII

FIGURE

PAGE

GONOCOCCAL INFECTIONS

1. Direct-view irrigating urethroscope for diagnosis and treatment	474
2. Janet-Frank syringe	482
3. Chetwood's irrigating nozzle	482
4. Kiefer's irrigating nozzle	482
5. Ultzmann's instillation syringe	483
6. Guyon instillation syringe	483
7. Oberländer's anteroposterior urethral dilator	492
8. Kollmann's urethral dilator; type used for dilating the anterior urethra	492
9. Kollmann's urethral dilator, anteroposterior dilating blades	493
10. Kollmann's urethral dilator, blades for dilating posterior urethra or prostate	493

CHAPTER XVIII

RABIES

1. Rabies tubercle in the medulla	546
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CHAPTER XIX

MALARIA

1. Chart showing malaria mortality by months	552
2. Relative prevalence of malaria in Arkansas, by months, as indicated by the number of cases reported	553
3. Blood index by years, to 20 years; first examination 31,459 persons	554
4. Blood index by age groups; first examination 31,459 persons	555
5. Chart showing the percentage of all the malaria found in the first blood examination of 31,459 persons, in each five year age group	556
6. Apparatus used in cultivation of malaria parasites	574
7. Different forms of malaria cultures	575
8. Resting positions of larvæ	582
9. Temperature chart of single tertian infection	588
10. Temperature chart of double tertian infection	589
11. Temperature chart of single quartan infection	590
12. Temperature chart of double quartan infection	591
13. Temperature chart of triple quartan infection	592
14. Temperature chart of tertian estivo-autumnal malaria	593
15. Temperature chart of quotidian estivo-autumnal malaria	594
16. Calls for malaria, 1916 (estimated) and 1917, Hamburg, Arkansas	621

FIGURE	PAGE
17. Showing the distribution of malaria as indicated by the intensity of the shading (America)	643
18. Showing the distribution of malaria as indicated by the intensity of the shading (Europe)	644
19. Showing the distribution of malaria as indicated by the intensity of the shading (Asia, Africa)	645

COLORED PLATES

PLATE	FACING PAGE
1. Quartan malaria plasmodia (<i>Plasmodium malarie</i>)	564
2. Tertian malaria plasmodia (<i>Plasmodium vivax</i>)	566
3. Estivo-autumnal malaria plasmodia (<i>Plasmodium falciparum</i>)	568

PRACTICE OF MEDICINE

VOLUME III

SECTION II

INFECTIOUS DISEASES (CONTINUED)

CHAPTER V

ACUTE LOBAR PNEUMONIA

By CHARLES R. AUSTRIAN, M.D.

Etiology, p. 2—Predisposing causes, p. 2—Exciting cause: the organism, p. 5—Morphology, p. 5—Cultural characteristics, p. 5—Differential cultural reactions, p. 6—Viability, p. 6—Virulence, p. 7—Toxin formation, p. 7—Biological classification, p. 8—Isolation of pneumococcus and determination of type, p. 9—Carriers, p. 10—Epidemiology, p. 11—Pneumococcus in apparently healthy individuals, p. 11—Pneumococcus outside the body, p. 12—Pathogenesis, p. 12—Immunity, p. 13.

Symptomatology, p. 15—General course of a typical case, p. 15—Clinical history, p. 16—Physical findings, p. 26—Laboratory findings, p. 29.

Diagnosis, p. 34—Differential diagnosis, p. 34—X-ray examination, p. 36.

Complications, p. 37—Association with other diseases, p. 48—Clinical varieties—types, p. 50.

Treatment, p. 54—Prophylaxis, p. 54—General measures, p. 54—Specific measures, p. 55—Vaccination, p. 55—General management, p. 56—Diet, p. 58—Hydrotherapy, p. 58—Aërotherapy, p. 59—Treatment of symptoms, p. 59—Specific therapy, p. 64—Serum therapy, p. 64—Vaccine therapy, p. 67—Chemotherapy, p. 68.

Prognosis, p. 69—Influencing factors, p. 69—Modes of death, p. 71—Duration, p. 71—Termination, p. 72—Relapse, p. 72.

Pathology, p. 72—Stages, p. 72—Distribution of the changes in the lungs, p. 74—Lesions in other organs, p. 74.

Historical summary, p. 75.

References, p. 76.

Synonyms.—Peripneumony (Hippocrates), pneumonia (Aretaeus), peripneumonia vera (Sydenham), pneumonic fever (Huxham), pleuropneumonia, croupous or fibrinous pneumonia, lobar pneumonia, pneumonitis, sthenic pneumonia, pulmonary fever, *pneumonie lobaire*, *fluxion de la poitrine*, *Lungenentzündung*, *kroupöse pneumonie*.

Definition.—Lobar pneumonia is an acute infectious disease due to the pneumococcus. It is characterized pathologically by an exudative inflammation of the lungs and clinically by distinctive local and general symptoms.

Though clinically an entity, lobar pneumonia may be caused by a

number of different microörganisms—a fact of fundamental importance in the prophylaxis and therapy of the disease.

ETIOLOGY

Lobar pneumonia may appear as a sporadic, an endemic or an epidemic disease, and though it is practically ubiquitous, certain main factors seem to govern its occurrence and spread.

Predisposing Causes.—**GEOGRAPHICAL DISTRIBUTION.**—Pneumonia occurs in all parts of the world, but is most frequent in the temperate zones and in regions with a wide daily range of temperature. It causes more deaths in North America and in Europe than does any other acute infectious disease.

COLD.—Experimentally it has been shown in animals that chilling of the body surface is followed by increased bronchial secretion and, at times, by actual bronchitis. Clinically the frequency with which respiratory infection follows upon exposure to cold and wet and the increased incidence of pneumonia during the winter months, among outdoor workers and in regions where there is a wide daily variation of temperature and humidity, are suggestive facts. But it is probable that the direct influence of cold has been overestimated, and its relation to subsequent respiratory inflammation may be more casual than causal. That it is not always a vital factor is evidenced by the rarity of respiratory disease among the members of Arctic exploratory expeditions and among those who live in cold, sparsely inhabited regions.

It may well be true that many of the cases of pneumonia that occur after chilling are dependent upon autogenous infection with pneumococci harbored temporarily in the mouth, and acquired by contact with pneumonic patients or with carriers.

CLIMATE AND SEASON.—The incidence of pneumonia shows a marked seasonal variation. It is greatest in the winter and early spring; less than twenty per cent of the cases develop in the summer, and an equal proportion in the autumn. The most important climatic conditions are abrupt changes in temperature and humidity, but the exact influence exercised by cold and moisture is poorly understood. The greater incidence of the disease in winter and in cold climates is undoubtedly influenced by the indoor life with resultant increase in the opportunity for contact infection and, perhaps, by the increased consumption of alcoholic drinks.

ALTITUDE.—The older view that altitude influences the morbidity and mortality rate of lobar pneumonia has been disproved by the statistics of the United States Army. It is said that cardiac complications are more frequent among those who live at high altitudes and intestinal complications more usual among those who live near sea level.

SEX.—Lobar pneumonia under ordinary conditions of life is more than twice as common in men as in women. That this difference of incidence is due to environmental conditions and to different degrees of exposure rather than to any especial susceptibility of the one or resistance of the other seems clear, for the higher incidence in the male is less evident in childhood and is not noted in institutions where the two sexes live under like conditions.

AGE.—Pneumonia occurs at all ages but is most common between

the ages of twelve and thirty-five years. Instances of congenital pneumonia are recorded. The mortality is greatest at the extremes of life.

RACE.—The morbidity and mortality are higher in the negro than in the white race, but it is not established whether this difference is due to a distinct racial character, to the lack of an inherited or acquired immunity to infection or to the poor hygienic conditions in which the negro lives. That the lack of an inherited immunity or the absence of immunity acquired by frequent minimum infections may be a vital factor is evidenced by the incidence of pneumonia among recently imported workers at the Panama Canal Zone, in the mines of the Rand, Africa, and by the decimation caused by the infection of Esquimaux and Lapps who migrate to temperate zones.¹

OCCUPATION.—In cities the incidence is greater among those who labor out of doors than among indoor workers. This difference cannot be explained on the basis of exposure alone, however, for it is not observed in rural communities. It may be dependent in part at least upon the class of workers in the contrasted occupations and on the poorer hygienic living conditions, with overcrowding and filth in the homes of the former group. The mortality is higher among indoor workers. Further, the susceptibility of newly inducted troops as compared with seasoned soldiers may be due as much to the overcrowding in the barracks or tents as to the unaccustomed exposure.

ACUTE INFECTIONS OF THE RESPIRATORY TRACT.—According to the histories, pneumonia was preceded by some acute infection of the upper respiratory tract in nearly fifty per cent of the cases we have observed. Undoubtedly, the incidence of such antecedent infections would be higher were an accurate record obtainable.

TOXIC AGENTS.—Lobar pneumonia has been known to develop following the inhalation of various irritating vapors, gases and the aspiration of different fluids. The action of these various substances may be in part mechanical, opening the way for infection. It would be interesting to study this group with reference to the incidence of pneumonia due to Type IV pneumococcus, for it is not improbable that the disease which results is dependent upon autogenous infection with the type organism already present in the buccal secretion. It seems more likely, however, that only those individuals who are carriers of the more usually pathogenic types develop the disease under these conditions.

The rôle of dust as an infecting agent has been demonstrated by Stillman,² who isolated virulent pneumococci from the dust of the environs of patients ill with pneumonia.

OVEREXERTION AND WORRY are predisposing factors only when so prolonged or marked as to cause general reduction of bodily nutrition.

TRAUMA.—True lobar pneumonia following trauma is exceedingly rare. It is most apt to follow crushing injuries to the chest or a direct blow with or without penetration of the thorax. The symptoms usually develop within a few days of the injury and the sputum is often more hemorrhagic than is the rule in the cases arising in the usual way.

PREGNANCY.—The relative infrequency of lobar pneumonia during pregnancy may be due to the limited exposure of pregnant women to infection, to the relatively low incidence in women or to a form of resistance the nature of which is not understood.

PREVIOUS ATTACK.—It is well known that an individual may have pneumonia several or more times; in fact, Norris records a history of

repeated attacks in the records of 13.6 per cent of the patients he studied. This happening has given rise to the erroneous view that infection with the pneumococcus is followed by a predisposition to reinfection rather than by an immunity. Cecil and Blake³ have demonstrated experimentally that monkeys convalescent from an infection with one type of the pneumococcus could not be reinfected with the same type of pneumococcus but that they were susceptible to infection with pneumococci of any of the other types. Thus it has been shown that the immunity and recurrent attacks of pneumonia in the same individual are to be regarded as due nearly always to different strains of the pneumococcus, each producing specific immunity to it, but not giving rise to immunity to the other strains. When several attacks of pneumonia due to the same type pneumococcus do occur in an individual, a focus of chronic infection should be sought for especially in the upper respiratory tract.

ALCOHOLISM.—It is questionable if alcoholism is an important predisposing factor except when it is excessive. The increased incidence of pneumonia among alcoholics is probably due more to exposure, general habits of life, etc., than to any direct influence of the alcohol itself.

ASSOCIATION WITH OTHER DISEASES.—*Typhoid fever* and lobar pneumonia rarely coexist. The term typhoid pneumonia should be restricted to designate pneumonia due to the *Bacillus typhosus* and not applied to pulmonary consolidation of different causation.

Influenza is frequently complicated by the development of pneumonia and the mortality is enhanced greatly thereby. The consolidation is usually lobular, often pseudolobar, occasionally true lobar in type. These pneumonias may be due to the streptococcus, the pneumococcus (most often Type IV) or to the influenza bacillus.

Pulmonary tuberculosis, according to Flick's statistics,⁴ is preceded by an attack of lobar pneumonia in nearly one-fifth of the cases studied. In the writer's opinion such an association is far less frequent, for careful analysis of the history will often disclose the fact that the acute initial symptoms were not due to a pneumococcus infection but to an acute tuberculous lesion clinically indistinguishable at the time from lobar pneumonia. Apical pneumonia and cases of delayed resolution may be confused with tuberculosis. Pneumococcus pneumonia is an uncommon complication of phthisis, and though it may not influence the course of many cases, it often leads to a recrudescence of a quiescent lesion and, at times, to the development of disseminated tuberculosis.

When lobar pneumonia develops in the course of *diabetes mellitus*, it has an exceedingly high death rate, and in these cases gangrene of the lung is a more frequent complication than it is otherwise.

In other chronic diseases pneumonia is a very usual terminal event, but it is much more frequently of the lobular than the lobar variety. When true lobar pneumonia does occur the onset is insidious, the course atypical and the mortality rate unusually high.

The relation of focal infections with the pneumococcus to the development of pneumonia has not been sufficiently studied. That there may be an important etiological relationship is evidenced by the cases of two patients, each with a chronic infection of a paranasal sinus due to Type II pneumococcus, both of whom developed subsequently a lobar pneumonia due to the same type organism.

Exciting Cause: the Organism.—The synonyms for this organism, as designated by various investigators, are: *Micrococcus pasteurii* (Sternberg), *Diplococcus pneumoniae* (Weichselbaum), *Pneumococcus* (Fränkel), *Microbe septicémique du salive* (Pasteur), *Micrococcus lanceolatus*.

Weichselbaum⁵ pointed out the fact that pulmonary consolidation may be caused by many different organisms, but the overwhelming frequency with which the pneumococcus occurs as the cause of lobar solidification of the lungs has led to the restriction of the term "lobar pneumonia" clinically to describe the disease due to that particular parasite.

This article deals only with pneumonia due to the pneumococcus. A consideration of the diseases due to infection of the lungs with various other microorganisms will be found in other sections.

In 1880, Sternberg isolated an encapsulated diplococcus from his own saliva, with which he produced a fatal sepsis in rabbits. Almost at the same time and independently, Pasteur made a similar discovery in the saliva of a child with rabies. Neither recognized the pathogenic properties of the organism at that time, and it is to Eberth,⁶ but more especially to Fränkel,⁷ that the credit is due for indicating the relationship of pneumococcus to pneumonia.

Fränkel demonstrated its frequent occurrence in lobar pneumonia, described its pathogenic and biologic characteristics and gave it the name by which it is most generally known. His findings were confirmed and elaborated by Weichselbaum, who identified the pneumococcus in the blood and the tissues of a large series of cases of pneumonia.

1. **MORPHOLOGY.**—The pneumococcus is typically a diplococcus; the individual members of each pair of cocci are lancet-shaped with flat surfaces opposed, but marked variations of size and shape are often noted, so that oval and bacillary forms may be seen in the same or in different cultures. In young actively growing cultures in fluid media chain formation may occur, but it is rarely seen when the growth is more sluggish and on solid media. In old cultures involution forms may scarcely be recognizable as the pneumococcus and even the characteristic staining reactions may be lost.

The organism is encapsulated, nonmotile and does not form spores. The capsule is most readily demonstrated in freshly isolated strains or when the young growth on suitable enriched media is examined. It appears as a halo about the cocci, and is pale or stained, depending upon the method of demonstration utilized. The capsule is most voluminous in the Type III *Pneumococcus mucosus*, and is well developed in recently isolated virulent strains of Type I and Type II, whereas in Type IV, though sometimes well formed, it may be scanty or absent. The function of the capsule is not definitely understood, though it is thought to be protective and may be an index of virulence.

The pneumococcus stains readily with the ordinary aniline dyes and is not decolorized by Gram's method (it is Gram-positive).

2. **CULTURAL CHARACTERISTICS.**—The organism can be grown on ordinary culture media but is very sensitive to variations in reaction and composition. Optimum conditions for luxuriant development are found when the media are prepared directly with infusion of beef, when sterilization is accomplished by the Arnold method and when the reaction is neutral or from 0.3 to 0.5 acid to phenolphthalein. The optimum temperature for incubation is 37° C. (98.6° F.), but growth will take place at a temperature as low as 25° C. (77° F.) and as high as

41° C. (105.8° F.). Its thermal death point is 52° C. (125.6° F.) for ten minutes. It is a facultative anaërobe and is not sensitive to changes of oxygen tension. On media prepared with beef extract the growth is scanty and poor, but on meat infusion agar enriched with blood the colonies are round, moist, discrete, translucent, with well defined edges. The center of the colony is darker than the granular periphery and the growth is surrounded by a zone of greenish discoloration.

The growth in broth is diffuse, leading to uniform turbidity of the medium; but after twenty-four hours, as autolysis of the cocci occurs the clouding clears. No pellicle forms, but there is flocculent sedimentation.

Gelatin is not a suitable medium for cultivation of the organism, but when pneumococcus is grown upon it, no liquefaction occurs.

In milk and in inulin-serum water the pneumococcus forms acid, with consequent coagulation of the medium. Fermentation of inulin is a characteristic property of pneumococcus utilized in the identification of the organism. Inasmuch, however, as some strains do not ferment inulin and others ferment it only at times, the test is of only confirmatory value and negative results are of little worth.

On media enriched with simple carbohydrates, the initial growth of pneumococcus is increased, but due to acid formation resulting from fermentation of the sugars, growth is inhibited early. The addition of calcium carbonate to such media will prolong the period of growth.

3. DIFFERENTIAL CULTURAL REACTIONS.—The pneumococcus is often difficult to differentiate from some strains of streptococcus, and to distinguish them certain cultural tests are especially helpful.

Colonies of pneumococcus on blood agar are surrounded by a green zone of methemoglobin.

Pneumococcus generally leads to fermentation of inulin, whereas streptococcus does not. Pneumococcus rarely causes precipitation in serum glucose agar (0.5 per cent glucose and ascitic fluid with a specific gravity of 1.015 or more), whereas streptococcus regularly does. The pneumococcus undergoes solution in bile due to the presence of cholic acid (Neufeld), whereas the streptococcus is not dissolved. This bile solubility test is recognized as a valuable differentiating character of the pneumococcus. The test may be carried out with whole bile or with a 10 per cent solution of sodium taurocholate or sodium glycocholate in 0.85 per cent salt solution. One-fifth to one-tenth volume of bile will cause solution of an actively growing broth culture of pneumococcus. The presence of serum inhibits the reaction, and avirulent strains are less constantly dissolved than are virulent ones.

The *Pneumococcus mucosus* forms a more abundant confluent, heaped-up sticky growth on the surface of solid media that characteristically "strings out" when a needle is raised from its surface. It is distinguished from *Streptococcus mucosus* by its solubility in bile, its power to ferment inulin, the greenish discoloration of blood media caused by it and its virulence for mice.

In brief, certain characteristics of the pneumococcus serve to differentiate it from allied organisms, especially the streptococcus. Finally, the specific reactions of various strains of pneumococci with their homologous immune sera definitely establish their identity.

4. VIABILITY.—The life of pneumococcus on artificial media is relatively short, and unless frequent transfers are made or special methods are employed the organism rapidly dies. Kept in the ice chest, cultures

in blood broth may remain viable for several weeks, and if the spleens of infected mice are dried *in vacuo* and kept in the dark, the organism may be recovered by animal inoculation after a period of months.⁸ Even on suitable media the pneumococcus sometimes fails to grow, but this is unusual if infected blood is added. Recent transfers to meat infusion broth grow poorly, but with frequent transplanting the organism grows more readily. Chesney has shown that transfers made during the period of maximum growth multiply readily and without the period of lag characteristic of older cultures.

5. VIRULENCE.—The virulence of the pneumococcus varies greatly. It is increased by passage through susceptible animals and attenuated by prolonged artificial cultivation. Recently isolated strains are usually very virulent for susceptible animals, but virulence is a relative term and varies for different hosts, so that an estimate of the infectivity of the organism for one animal is not necessarily a measure of its invasiveness for another. It is only generally true that a given strain of pneumococci virulent for man will be virulent for mice, and *vice versa*.

To what extent the increased or decreased incidence of pneumonia is dependent upon variations in the virulence of the pneumococcus has been the subject of much discussion. The fact that the invasive power of the organism may be enhanced by passage through animals and lessened by prolonged artificial cultivation offers some support for this idea. But virulence is *not* absolute; it is relative to and dependent upon the resisting power of the host, which may vary as widely as the invasive ability of the organism. Outbreaks of pneumonia are surely determined as much by variations in the susceptibility of the invaded as by the virulence of the invader—a fact admirably illustrated by the case of healthy carriers who may harbor pathogenic types of the pneumococcus without developing pneumonia.

6. TOXIN FORMATION.—It has not been shown that the pneumococcus forms a true soluble toxin, and the manifestations of pneumococcus infection are variously attributed to the action of liberated endotoxins, to intoxication with poisonous split products resulting from the disintegration of bacterial protein and to the products set free by the metabolic activities of the organism itself. Autolysates of the cocci are hemolytic and toxic, and though both of these properties are lessened by the action of immune serum, neutralization is not complete nor is it absolutely specific. Both the lytic and the anaphylatoxic action vary with the virulence of the organism and both are thermolabile, removed by filtration through a Berkefeld filter and by tryptic digestion. According to Dochez and Avery, the hemotoxin exists preformed in the bacterial cell as a hemolytic endotoxin.

Recently these observers have confirmed and extended the observation of Kraus⁹ on the formation by the pneumococcus of a soluble substance in culture media. This specific precipitable substance found in the cell-free fluid of young cultures not only is demonstrable *in vitro*, but is present also in the blood and urine of infected animals and of patients with pneumonia. It is thermostable and is not destroyed by precipitation with alcohol, ether or acetone, or by digestion with trypsin.¹⁰

The demonstration of this substance in the blood and urine of infected individuals is of real diagnostic and prognostic value, and when it is excreted in large amounts is a sign of unfavorable import. To what extent this precipitable substance may be responsible for the in-

toxication present in infections with pneumococcus is not established.

7. BIOLOGICAL CLASSIFICATION.—Neufeld and his co-workers first clearly indicated that groups of pneumococci could be differentiated from one another by their immunologic reactions, and Dochez, Cole and his associates at the Hospital of The Rockefeller Institute established the differentiation of the species into four definite types. Lister has further refined the classification.

The classification is made on immunological and cultural tests and on morphological characters. Pneumococci isolated from numerous cases of pneumonia were studied; animals were immunized to each of many strains; and the immunity reactions of all were tested against each serum thus obtained. Agglutination, precipitation and protection experiments clearly established the existence of at least four groups of organisms arbitrarily designated Types I, II, III and IV. Individual members of Types I and II show no distinctive morphological or cultural properties, but each possesses immunologic characters common to other members of the homologous group and different from those of other groups. Many atypical strains of Type II have been studied but the significance of this finding is not established. Type III is the *Pneumococcus mucosus* and it is distinguished from the other types by morphologic and cultural differences as well as by immunologic reactions. All members of this type provoke a common immunity response.

Type IV consists of heterogeneous strains that are not interrelated, and only small groups of this type have common immunologic properties.

Types I, II and III include about 80 per cent of all strains responsible for infection in man. Type IV includes about 20 per cent of the strains isolated from lobar pneumonia and is the variety generally found in the buccal secretions of normal individuals.

PNEUMOCOCCUS	INCIDENCE
Type	Per cent
I	33.3
II	29.3
II Atypical	4.2
III	13.0
IV	20.3

From this table of Avery, Chickering, Cole and Dochez,¹¹ it is seen that Types I and II are the usual cause of infection and are responsible for over 60 per cent of the cases of lobar pneumonia studied. Type III is an infrequent cause of infection, and Type IV is the etiological agent in about 20 per cent of the cases, the incidence of disease due to it varying in different places.

According to Cecil, Baldwin and Larsen, young people are especially liable to infection with pneumococcus Type I and elderly people to infection with pneumococcus Type III, whereas there is no relation between age and the predilection to infection with Types II and IV.

The relative incidence of infections due to the several types varies from year to year and this is undoubtedly a factor in determining the differing mortality noted in epidemics.

Immunization of horses with strains of Type I or II results in the development of a serum of reasonably high titer. Such sera are efficacious against members of the homologous group, but are without pro-

tective value against individuals of the other type. Immunization with Type III has not yielded a satisfactory protective serum, and though comparatively potent sera can be developed by inoculations of members of Type IV, such sera protect only against the organism used to produce them and lack the power to prevent the progress of infection due to other members of the same type.

The identification of the particular type of pneumococcus responsible for infection in large numbers of cases has led to a revision of our ideas of the epidemiology of lobar pneumonia, and it furnishes a better basis for prognosis and for specific therapy in individual cases.

8. ISOLATION OF PNEUMOCOCCUS AND DETERMINATION OF TYPE.—

A. *From Sputum*.—(i) Stained Smear Preparations.—Direct spreads of sputum are stained by Gram's method and with a capsule stain. The pneumococcus is readily recognized by its morphology and Type III may be identified by its very abundant capsule.

(ii) Mouse Inoculation.—The sputum is carefully washed in several changes of sterile salt solution to free it of contaminating organisms and a small bit is then emulsified with sterile broth or salt solution. With aseptic precautions 1 c.c. of this emulsion is inoculated into the peritoneal cavity of a white mouse and as soon as the mouse appears ill, a drop of peritoneal exudate is removed by aspiration. If smear preparations show very numerous pneumococci the animal is killed and the determination of type is made; if the organisms are few the animal is allowed to live and later test aspirations are made, or the animal is allowed to die. At autopsy the peritoneal cavity is opened with sterile precautions and both cultures and films made from the exudate to prove the pneumococcus is present in pure culture.

A modification of this method of value rapidly to identify the type of a given strain of the micrococcus was reported in 1929 by Park. Four or five hours after a mouse has been inoculated intraperitoneally with a suspension of the organism, several drops of the peritoneal exudate are mixed on a glass slide with an equal amount of the several known type sera, the preparation is stained with fuchsin and examined with the microscope. The demonstration microscopically of agglutination according to this technic makes possible within a few hours the typing of a given strain of pneumococcus.

The organism should be identified also by cultural tests. The peritoneal exudate from the mouse is washed out with sterile salt solution and the washings are centrifuged at low speed to remove the fibrin and cells. The supernatant bacterial suspension is transferred to another tube and centrifuged at high speed until the pneumococci are sedimented. The fluid is then decanted and the bacterial sediment is taken up in sufficient salt solution to make a suspension of about the opacity of an 18-hour broth culture of the organism. Fractions of this suspension are used for macroscopic agglutination tests, being mixed with dilutions of immune serum in equal quantities. The concentration of serum required will vary with the titer of the serum employed, but it is necessary that the dilution be found which causes agglutination of the homologous type and does not cause cross-agglutination of the other types before a given serum can be utilized in carrying out the test.

The agglutination test is not satisfactory when other organisms are present in large numbers; and when this is the case the precipitin method, as described by Blake, should be utilized.

The peritoneal exudate prepared according to this technic is immediately centrifuged at high speed until the supernatant fluid is water-clear. The clear fluid is mixed in quantities of 0.5 c.c. with equal quantities of antipneumococcus serum and a specific precipitation promptly occurs in the tube containing the homologous immune serum. This test is consistently positive with Types I, II and III and negative with Type IV. To identify the atypical strains of Type II it is necessary to use two dilutions of serum in the test. The typical Type II causes precipitation in both diluted and undiluted serum, whereas variants in this type precipitate only the undiluted serum. The precipitin test is not interfered with by the presence of other organisms.

B. From Blood Culture.—Cultures of the blood are made as described, and the organism identified as the pneumococcus. Ten c.c. of the infected blood broth are centrifuged at low speed to remove blood cells and the supernatant fluid transferred to another tube. This is centrifuged at high speed and the sedimented bacteria are resuspended in sterile salt solution. The type of pneumococcus is then determined by macroscopic agglutination tests.

C. From Spinal Fluid, Empyema and Lung Puncture.—The type of pneumococcus obtained from these sources is determined according to the foregoing methods.

Lung puncture is a procedure to which recourse need rarely be had, but when it is carried out cultures should be made directly in bouillon.

D. Determination of Types of Pneumococcus by Means of Specific Precipitin Reaction in the Urine.—Reference has already been made to the fact that a certain percentage of patients with lobar pneumonia excrete in the urine at some stage of their disease a soluble precipitable substance of pneumococcus origin. This substance gives a specific precipitin reaction with antipneumococcic serum corresponding in type to the organism causing the infection. The test for it does not supplant the usual bacteriological methods, but is useful in that in some cases an immediate diagnosis of type can be made from a study of the urine.

The urine, concentrated or as passed, is centrifuged and when water-clear is mixed in amounts of 0.5 c.c. each with equal quantities of antipneumococcic serum of the various types. A precipitate is formed immediately or after incubation for one hour at 37° C. (98.6° F.). The reaction may be slight or marked. Long incubation should be avoided as bacterial growth may obscure the result.

9. CARRIERS.—Ever since the observations of Pasteur and of Sternberg, it has been known that the pneumococcus is present in the mouths of many healthy people, but it is only of recent date that the importance of this fact has been appreciated in studying the epidemiology of pneumonia. It is now generally conceded that the types of pneumococcus ordinarily harbored in the buccal secretions of the healthy are the more or less saprophytic Type IV, the infrequent Type III and atypical Type II, relatively uncommon causes of lobar pneumonia; and that in the healthy the more pathogenic types are not usually found. But often in those convalescent or recently recovered from the disease, in those intimately exposed to patients with pneumonia and very rarely in a healthy individual who has not been in contact with the disease, the more parasitic Type I and Type II are present. These individuals—and of them more particularly the convalescent and those intimately

exposed to the disease—are real carriers, and it is probable that through their agency the disease is often spread.

10. EPIDEMIOLOGY.—Epidemics of pneumonia are not uncommon and the statistics collected by Wells admirably indicate the special peculiarities of many of those that have occurred. The reported outbreaks were noted most commonly in the winter and spring, and were rarely extensive except in barracks, prisons and hospitals.

The epidemiological studies of Stillman indicate that the disease is spread directly through contact of the healthy with patients ill with pneumonia, with carriers healthy and convalescent and through infected dust; and they emphasize the need of isolation to prevent the dissemination of the disease.

11. PNEUMOCOCCUS IN APPARENTLY HEALTHY INDIVIDUALS.—Extensive observations have shown that the pneumococcus occurs in the buccal secretions of the healthy in from 15 to 85 per cent of all cases examined. Longcope and Fox showed a low incidence for November, an exceedingly great increase in December and January and a slow return to a low incidence in March and April.

The frequency with which pneumococcus occurs in the saliva is independent of the place of residence and the kind of occupation but, according to Buerger, the organism is found more often in males than in females.

Dochez and Avery¹² showed that a large percentage of individuals in intimate contact with active cases of lobar pneumonia, due to infection with Types I and II pneumococci, harbor in their buccal secretions organisms of the type responsible for the disease. They likewise demonstrated the infrequent occurrence of these highly parasitic types in any except those exposed to infection or in those convalescent from pneumonia.

Stillman,¹³ in elaborate epidemiological studies based on these findings, studied the saliva of 942 healthy individuals, some in contact with lobar pneumonia. From the saliva of 450 (or 47 per cent), one or more types of pneumococci were isolated; and from 492 individuals no pneumococci could be recovered at the time of the examination. The appended table summarizes the frequency of occurrence of the various types:

PNEUMOCOCCUS	INCIDENCE	INCIDENCE
<i>Type</i>	<i>No.</i>	<i>Per cent</i>
I	34	7.0
II	22	4.5
IIa	1	0.2
IIb	26	5.3
IIx	47	9.7
III	85	17.5
IV	271	55.8
Pneumococcus present....	450	
“ absent	492	
	<hr/> 942	

In view of these studies it is clear that Types IV, III, IIb and IIx must be regarded as normal inhabitants of the healthy mouth, and that

Types I and II rarely occur in the saliva, except of those convalescent from infection or of those exposed to the disease lobar pneumonia. The latter fact is borne out by the demonstration of these types in only 0.8 per cent of the healthy as compared with an incidence of 11 per cent in the mouths of those convalescent or recently recovered from pneumonia and in those individuals who have been in contact with them.

These data indicate the epidemiological importance of contact as a means of disseminating the disease and show that it may be spread by associating with patients, convalescents, healthy carriers or through the agency of infected dust. They show further that the types responsible for most of the cases of pneumonia are rarely demonstrable in healthy people who have not been exposed to the disease.

If autogenous infection with one of the types normally present in the mouth occurs, it is due to altered resistance of the host as often perhaps as to enhanced virulence of the micrococcus or to a combination of these two factors.

12. *PNEUMOCOCCUS OUTSIDE THE BODY.*—The pneumococcus is a very delicate organism and soon dies outside the body. Even in cultures it succumbs rapidly unless conditions are optimum. It is readily killed by exposure to sunlight, by treatment with ordinary disinfectants and by heat. In sputum it is fairly resistant.¹⁴ In moist sputum at room temperature and in the dark the organism has an average viability of about fourteen days; in strong light of less than five days. At 0° C. it may live 35 days, but when moist it is killed by exposure to 52° C. (125.6° F.) for ten minutes.

In powdered sputum the pneumococcus dies in from one to four hours, depending upon the exposure to light. In dried sputum in the dark it survives on an average for 35 days; in diffuse light 30 days; but in direct sunlight less than four hours.

According to Stillman, the pneumococcus was demonstrable in the dust of patients' quarters in over 53 per cent of the cases studied, and in every case the same type was present in the dust as was responsible for the illness. Growth developed in cultures of dust as long as 16 days after the patient was removed from the source where it was obtained, but generally the dust became free of pneumococci sooner than did the saliva of individuals exposed to the disease.

13. *PATHOGENESIS.*—The why of infection with, and the wherefore of resistance of particular individuals to, the pneumococcus are still moot. The usual mode of infection, the route by which the micrococcus reaches the lungs, are questions that await still final determination.

The aspiration or inhalation theory is the one accepted generally and there is much evidence to support it. The frequency with which an acute infection of the upper respiratory tract antedates the onset of pneumonia, the epidemiological studies of Stillman, the insufflation experiments of Lamar and Meltzer,¹⁵ the instances of so-called anesthesia or aspiration pneumonia, all point to the aërogenous transmission. The experiments of Cecil and Blake¹⁶ validate this view even more definitely. They demonstrated that when virulent pneumococci are injected into the trachea of monkeys, an inflammatory reaction is set up in the interstitial portions of the lungs which advances from the hilum by way of the peribronchial and septal tissues and lymphatics and extends finally into the alveolar spaces synchronously with the formation of an exudate in the alveoli.

Granted a primal and aërogenous route of infection with the pneumococcus, the fact that pneumonia has not been produced experimentally when the microorganisms were introduced into the upper respiratory tract has led to the view that the aspirated bacteria are transported to the lungs by a circuitous route. It has been suggested that they enter the capillaries—vascular and lymphatic—of the upper respiratory tract and that they reach the lungs by a hematogenous or by a lymphogenous way. This predicates usually the occurrence of a bacteremia as an antecedent to the development of pulmonary consolidation, and instances have been cited in which pneumococci have been grown in cultures of the blood before the signs of pulmonary consolidation have developed. However, such evidence is not conclusive for, as is well known, the local pathological manifestations of early localized consolidation of the lungs may be overlooked. More suggestive, perhaps, are the disproportions between the constitutional symptoms and the extent of the local inflammatory changes in the lungs noted in many patients, the occasional occurrence of a so-called primary settling of the pneumococcus in the meninges or in the peritoneum and the analogy with epidemic cerebrospinal meningitis.

14. IMMUNITY.—An epidemic and endemic disease, self-limited and usually terminating abruptly, pneumonia apparently offers problems in immunity that should be readily solved, but study has shown the case to be otherwise.

The relative resistance of man to infection with the pneumococcus, as evidenced by the infrequency of a sepsis without metastatic localization, has been attributed by some (Dold) to opsonins and bactericidal substances occasionally present in the serum of normal individuals. But this thesis is negated by the absence of increased protective power of the serum of those recovered from pneumonia, in which these bodies are more constantly and more abundantly present.

The immunity that develops in favorable cases of the disease is understood better, and study of the phenomena associated with crisis has cast light upon the whole subject of immunity to the pneumococcus. It is known that crisis is not due to anatomic changes in the lung or to a sudden loss of virulence of the pneumococcus (Rosenow); that the percentage of positive blood cultures and the intensity of the blood invasion, if present, decrease as crisis or lysis is approached, and that the number of viable organisms that can be isolated from material obtained by puncture of the lung diminishes perhaps even to zero during or after crisis.

The literature abounds with contradictory explanations of the conditions responsible for the production of these changes and for the protection produced experimentally in animals.¹⁷⁻²³ According to Clough,²⁴ the only antibodies that appear in significant quantities are substances that promote phagocytosis. He has shown that serum obtained after crisis causes active phagocytosis of the homologous virulent strain and that with the increased phagocytic power of the serum there is a parallel increase of its power to protect mice against infection with the homologous type.

Inasmuch as the phagocytic activity of such serum parallels its protective power for mice in time of appearance, incidence and in strict specificity, it would seem that the protective power depends upon and is due to its power of producing phagocytosis.

A state of hypersensitiveness to the protein of pneumococcus has

been demonstrated in some cases of pneumonia, but its development is inconstant. It does seem, however, that an allergic state may be responsible for many of the manifestations of the disease. The predominantly exudative character of the local reaction, its intra-alveolar, non-interstitial localization and the abrupt onset all resemble the type of response caused by experimental infection in sensitized animals.

Finally, although bacteriotropins, agglutinins, lysins, opsonins and other antibodies may each in varying degree contribute to the immunity against the pneumococcus, the exact rôle played by each has not been established.

Individual immunity depends upon a number of factors—activities of the leukocytes and of the alveolar epithelium, agglutinins, precipitins, opsonins, complement-fixing substances and so-called “protective bodies.” The last are substances which prevent the death of mice that are injected simultaneously with them and with an otherwise lethal dose of virulent pneumococci. These bodies, like other immune bodies, are highly specific and are demonstrable usually in the blood of patients at or just before the time of crisis. In addition, Avery has shown that in pneumonia a so-called “soluble substance” is formed that, like the “protective bodies,” is specific for each type of pneumococcus, is nontoxic and nonantigenic but is capable of neutralizing the immune substance formed by the patient. It is a polysaccharide present always in the filtrates of cultures of virulent pneumococci and is found often in the blood of patients with pneumococcic sepsis, in the urine of severe cases of pneumonia and in the purulent exudate of empyema. It originates in the capsule of the microorganism and enhances the virulence of the latter by preventing the phagocytosis of it.

One of the important functions of the immune bodies is to prevent the entrance of the pneumococcus into the general circulation. In those who die of pneumonia, these bodies are rarely demonstrable and sepsis is frequent. Large amounts of Avery's soluble substance are present in the serum and in the urine of such patients, and one may infer that the immune bodies were neutralized by it with a resultant invasion of the blood stream of the pneumococcus.

Clough,²⁴ Blake,²⁵ and Robertson and Sia²⁶ have demonstrated that the immune bodies, like opsonin, are necessary for the phagocytosis of virulent pneumococci, and, as it has been shown that the final destruction of pneumococci is accomplished by the leukocytes, the important rôle played by these antibodies becomes apparent.

Just as the protective bodies favor phagocytosis, so the soluble substance of Avery interferes with this activity of the leukocytes by neutralizing the immune bodies and permits the pneumococcus to maintain its virulence.

In infections with the pneumococcus, the ultimate outcome depends on whether the pneumococci or the leukocytes gain supremacy. If the patient produces enough immune bodies, the infection will be kept localized in the lung and recovery will probably follow. Contrariwise, if the pneumococcus produces the soluble substance in amounts more than sufficient to neutralize the immune bodies, phagocytosis is prevented, infection spreads, pneumococci invade the general circulation and the patient dies with a pneumococcus sepsis.

SYMPTOMATOLOGY

General Course of a Typical Case.—The disease usually sets in abruptly, generally with a rigor. This is of variable duration, occasionally lasting an hour or more. During it there is apprehension, the teeth chatter, there is generalized shivering, the patient complains of feeling cold and is so ill he takes to bed. The chill gradually subsides and in place of a feeling of cold, a sensation of unbearable heat comes on. The skin and mucous membranes, pale during the rigor, become flushed and red, a throbbing headache often develops, and either torpor or delirium may appear. There is anorexia and oftentimes vomiting. The temperature is elevated and may rise to 104° or 105° F. (40° or 40.6° C.).

Usually at onset or after the rigor there is intense thoracic pain increased by respiratory effort—deep breathing, laughing, coughing, yawning or sneezing—so severe as to cause cessation of all voluntary activities. The respirations are rapid, superficial, often slightly irregular, labored and interrupted by a dry, hacking cough.

The patient is manifestly ill and the history, with the finding of dyspnea, flushed skin and often cyanosis, bright, glistening eyes, rapid, shallow respiration, expiratory grunt, dilatation of the nostrils with each breath, accelerated pulse, fever, the complaint of thoracic pain and the hacking cough, arouses the definite suspicion of a developing pneumonia. Examination of the lungs, however, may discover only limited expansion of one side of the chest, suppressed breath sounds or a pleural friction rub.

After 24 to 72 hours the thoracic pain diminishes in intensity, the cough becomes productive, leading to the expulsion of characteristic sputum, herpes appears on the lips or other parts of the face, the fever continues at the same or at a higher level, the tachycardia is unchanged and a tympanitic note is elicited over an area of the chest where, too, there may be suppression of breath sounds, crepitation or tubular breathing.

In mild cases these symptoms persist for several days. By the sixth or eighth day they may become more marked, the pulse more rapid and weaker, the cyanosis more pronounced, while outspoken signs of consolidation of the lung that have developed may spread or resolution may begin.

At a varying period after onset the crisis may occur. The temperature suddenly falls, reaching normal in 10 to 24 hours, beads of perspiration appear on the face and soon the entire body is bathed in a copious sweat. Respiration becomes easier, slower, less labored, the color improves and the disagreeable symptoms associated with fever disappear. The sensorium clears and the patient passes from a state of extreme illness and discomfort to one of comparative well-being.

In more severe cases crisis fails to develop, dyspnea and cyanosis increase, the temperature continues high or, though it falls even to normal, the condition of the patient does not improve. The pulse becomes more rapid and weaker, restlessness and anxiety develop and collapse follows.

In other instances crisis is delayed or never occurs, and a case with mild symptoms may suddenly develop very grave and untoward manifestations.

Clinical History.—**INCUBATION PERIOD.**—The period of incubation is not definitely established. It is probably short and is variously estimated at from one to eight days. Of especial value in the determination of the time for incubation are the cases in which pneumonia follows trauma. In observed instances the time between the injury and the chill of onset has varied from a few hours to one or two days.

PRODROMAL SYMPTOMS.—Prodromal symptoms are generally lacking, though not infrequently a history is obtained of antecedent thoracic pain, anorexia, headache, lassitude, an acute bronchitis, vomiting, tonsillitis, joint and muscle pains, epistaxis, abdominal pain, etc.—none of which is characteristic. The most common prodrome is a mild acute respiratory infection. The frequency with which such a history is obtained will depend in large measure upon the care with which the investigation is made.

ONSET.—The onset with chill is by far the most frequent. According to Norris,²⁷ of 9,851 cases, 58.18 per cent had a rigor; of 2,334 cases, 30.12 per cent had chilliness; of 217 cases, 12.44 per cent had repeated rigors. Jurgenson states that 60 per cent of all cases have either a chill or chilly sensations at the onset.

The presence or absence of this symptom depends upon the individual attacked and upon the type of the infecting pneumococcus. It is uncommon in children, in whom a convulsion is of more frequent occurrence; and in the aged, asthenic or alcoholic it is often lacking. In the latter groups the onset is gradual in about half of the cases. A true rigor occurs most frequently in cases of infection with pneumococcus Type I (70 per cent) and least frequently in those due to pneumococcus Type IV (55 per cent²⁸).

The rigor of onset may last as long as nine hours (Nothnagel) and it may be repeated.

SYMPTOMS DURING PROGRESS OF DISEASE.—(a) *Fever.*—During or just after the initial chill the temperature rises abruptly and reaches its summit on the first or second day. In cases that have no chill at onset the temperature may rise rapidly, but occasionally the ascent is slower and may continue 3 or 4 days before attaining a maximum.

As a rule, the fever remains at a fairly constant level from onset to crisis with small remissions of 0.5°–1° F. (0.3°–0.5° C.) in the twenty-four hours. The average maximum is 103° F. (39.4° C.), though in many cases a higher level is maintained and a temperature of 105° or 106° F. (40.5° or 41.1° C.) is not uncommon.

Instead of a continued or subcontinued elevation of temperature, the fever may be outspokenly remittent, with a daily range of 1.5°–3° F. (0.8°–1.6° C.). Less often an intermittent fever with oscillations of 4 or more degrees above and below the base line is seen.

A relapsing type of fever has been described (Wunderlich). It was formerly seen in patients treated by repeated liberal venesections.

Abrupt exacerbations of fever sometimes occur, accompanying the spread of the inflammatory process to portions of lung hitherto uninvolved, and similar rises, apparently independent of any extension of the disease, occur.

A sudden fall of temperature with collapse may occur at any stage of the infection and is to be differentiated from a pseudocrisis by the associated physical signs (poor quality of the pulse, appearance of the patient, etc.).

Pseudocrisis is a term used to describe a marked abrupt lowering of the temperature occurring, as a rule, one to three days before the true crisis and accompanied by an improvement in the general condition of the patient. It is distinguished from a *real crisis* by less marked slowing of the pulse rate and by a subsequent rise of temperature within 24 to 48 hours. Pseudocrisis occurs in about 10 per cent of all cases of pneumonia.

Defervescence in typical uncomplicated cases is by crisis. The fall of temperature comes on abruptly from a maintained high level or from some point in a scale of gradual descent, and reaches normal within 24 hours. Occasionally the crisis is preceded by a slight or a marked exacerbation of fever. If the fall to normal requires more than 24 hours it is termed a *protracted* or *delayed crisis*; if more than two days elapse, termination of fever is said to be by *lysis*. The critical fall in temperature begins most often in the evening or during the night and may be extremely rapid. The writer has seen a fall of 4.5° F. (2.5° C.) in six hours.

The day of disease on which *crisis* occurs varies greatly. Traube's dictum that it occurs only on the odd days—third, fifth, seventh, ninth, eleventh—has long been discredited, and collaborated statistics show a nearly equal incidence on the odd and even days. Crisis as early as the beginning of the second day and as late as the sixteenth has been observed by the writer. It has been known to occur later than the twentieth day (Norris), but most commonly it occurs between the fifth and the thirteenth.

After crisis, a subnormal temperature may persist for several days, but hypothermia is much less common than in convalescence from typhoid fever. Marked postcritical elevations of temperature, except in association with a complication, are rare; but it is the rule for days or weeks after crisis has taken place to have an elevation to 99° or 99.5° F. sometime in the twenty-four hours. These slight elevations are perhaps associated with absorption from the resolving exudate in the lung.

When defervescence has not been established by the 14th day it is apt to take place by lysis. Lysis occurs in about 20 per cent of all cases, and is especially common in the aged and in secondary pneumonias.

Unusual grades of hyperpyrexia [107°–109° F. (41.6°–42.8° C.)] have been recorded in association with marked nervous symptoms and just before or even after death. Parkinson²⁹ reported a case of pneumonia without nervous symptoms in which a temperature of 110° F. (43.3° C.) was recorded on the 5th day of the disease and an elevation of 105° F. (40.5° C.) for four days, after which crisis occurred.

(b) *Thoracic Pain*.—Thoracic pain is the most constant local symptom of pneumonia, occurring in about 90 per cent of all cases (Grisolle). It is frequently the initial symptom, antedating the chill of onset by several hours; it often begins during the rigor or it may rarely develop in the course of the first days of the attack. It is most intense during the early hours and usually disappears within the first several days. The very prompt subsidence of the pain is occasionally an unfavorable sign, indicating the development of a pleural exudate.

The pain is a typical "stitch in the side" associated with inflammation of the pleura. It is variously denoted as intense, sharp, stabbing or lancinating, and is so agonizing that the patient voluntarily shortens the depth of inspiration. The severity of it is not an index of the

gravity of the disease, though oftentimes it is of maximum grade in the severer cases.

The pain is rarely diffuse but is localized in a portion of one side. It occurs most commonly in the lower axillary or in the mamillary region, but may appear in any part of the chest or shoulder. There is at times hyperesthesia of the skin over the painful area, and circumscribed pressure increases the pain, whereas broadly applied pressure often relieves it. The reason for the apparently paradoxical influence of pressure is probably the fact that the wider application, by limiting expansion, lessens the mobility of the lung.

In children pain is often absent, though at times it may be exquisitely severe. In the aged, the asthenic, the alcoholic and the delirious it is often lacking, and in central and in apical pneumonia it is a very unconstant symptom.

The cause of the pain is probably not pulmonary in origin, as evidenced by its absence in extensive disease of the lungs (neoplasm, deep abscess, etc.), but it is usually ascribed to the inflammation of the pleura associated with the pneumonia.

The pain may be migratory in character; it may be referred to the uninvolved side of the chest, to the shoulder, neck, arm or abdomen.

(c) *Abdominal Pain*.—Abdominal pain is not uncommon in pneumonia.^{30, 31} The importance of the recognition of it as a symptom of this disease cannot be emphasized too strongly because of the errors of diagnosis to which ignorance of this fact may lead. The pain may be referred to the upper or lower quadrants of the abdomen and unfortunately it has happened often that the source of it has been misinterpreted. More than a few patients with pneumonia have undergone laparotomy for a suspected appendicitis, cholecystitis, cholelithiasis, peritonitis, etc., when subsequent events have clearly shown that the abdominal symptoms were due solely to the intrathoracic disease. The coincident presence of rigidity and even of spasm of the abdominal muscles may make differential diagnosis extremely difficult, but a carefully taken history and the presence of rapid, shallow respiration, cyanosis, herpes labialis, etc., will disclose usually the cause of the symptoms.

Chatard,³² in his analysis of 658 cases at the Johns Hopkins Hospital, noted the occurrence of abdominal pain in 77 per cent.

The cause of the abdominal pain is attributed generally to the existence of a diaphragmatic pleurisy.

(d) *Respiratory Tract*.—*Tachypnea*³³ is practically an invariable accompaniment of lobar pneumonia, and whenever—especially during the winter months—it is noted pulmonary consolidation should be suspected. The respiratory rate is accelerated to rates varying from 20 or 24 to as high as 80 or 90 breaths per minute, and to as high as 200 in infants. The average for adults is between 24 and 40 in an attack of moderate severity, and when a rate of more than 50 to 60 per minute is encountered in an uncomplicated case, it is a cause for apprehension.

The respirations are rapid, shallow, the patient grunts with each expiration, speech is difficult, and the *alæ nasi* actively play.

Accompanying tachypnea there is nearly always *dyspnea* of greater or less severity. When dyspnea is present to a degree out of proportion to the extent of the consolidation, it is a sign of grave omen.

Rapid and difficult breathing, when occurring in association with

great pain and marked psychomotor agitation, is less significant than when signs of cardiac embarrassment are present.

The tachypnea and dyspnea are due to a combination of factors. Pain causes voluntary and involuntary restriction of respiratory effort, thereby hastening breathing and rendering it difficult. Toxemia, cyanosis and nervous symptoms also play a rôle. The influence of the extent of pulmonary involvement is still moot. Undoubtedly it is of some moment, but the observations of Washburn on experimentally infected mice, the results of postmortem studies in many cases, of intravital examinations in others and the disappearance of these symptoms after crisis while the consolidation is still unchanged, indicate it is not the determinant of their existence except perhaps in bilateral pneumonia.

Finally, the rôle of acidosis as a cause of the polypnea and dyspnea seems established. Lewis³⁴ and his coworkers have definitely shown that an acidosis due to nonvolatile acids is responsible for these symptoms in the cases without cyanosis and to a lesser degree is causal in those with cyanosis. They showed that in pneumonia and in extrapulmonary pneumococcal lesions the alveolar air has a high oxygen content, a low percentage of carbon dioxide and an increased hydrogen-ion concentration due to nonvolatile acids in the blood. Such acidosis, when of mild grade, persists over the crisis, to vanish hand in hand with the breathlessness as convalescence is established. These observations also indicate that the respiratory symptoms of pneumonia cannot be attributed solely to the extent of lung damage.

Cyanosis.—Lundsgaard³⁵ demonstrated that the fundamental cause of cyanosis is an abnormal amount of reduced hemoglobin in the blood within the capillary circulation. In pneumonia this results from the insufficient oxygenation of blood passing through the unconsolidated portions of the lungs and probably not because of the passage of blood through the unœrated pulmonary tissues of the pneumonic areas.

Cheyne-Stokes breathing is an untoward symptom that occurs especially in the cases with grave toxemia and cardiac failure.

Cough is generally present from the onset and, when bronchitis precedes the chill, is present before it. At first it is unproductive and occurs in paroxysms, but it soon becomes frequent, is accompanied by great pain, and every effort is made to suppress it. Later in the course—and especially after crisis—the paroxysms are more prolonged, easier and more productive.

Frequently recurring paroxysms harass the patient, causing pain, restlessness, anxiety and loss of sleep. The violent muscular efforts lead to muscle soreness and throw a severe strain on the right heart. When the cough is especially violent it may lead to exhaustion and collapse.

Cough is more frequent in pneumonia of the lower lobes; it is less constant or even lacking in secondary pneumonia and in pneumonia of the aged, the very young, the alcoholic and very delirious patients.

Cough persisting or developing after crisis is sometimes indicative of a developing pleural exudate, especially empyema.

Sputum.—In no other disease except bronchial asthma are the gross properties of the sputum and the cycle of changes through which it evolves so characteristic as in lobar pneumonia. Especially when bronchitis precedes the onset of an attack, the sputum is mucoid and abundant for the first four or five days. Then, as the inflammatory process spreads and leads to involvement of the alveoli of the lung, it becomes bloody,

due to the presence of red corpuscles. Soon it becomes so characteristic as to be diagnostic. Rusty, homogeneous, transparent and extremely tenacious, it must often be wiped from the lips and clings to the inverted container into which it is expelled. Blood is constantly present, uniformly mixed with the mucoid material, rarely in streaks. Occasionally the sputum is pure blood. The amount varies considerably but, according to Emerson, 150-300 cubic centimeters is the daily average.

The color is a rusty yellowish-brown, but it may be yellow, green, orange, etc., as the hemoglobin derivatives that give it color undergo oxidation. The fact that the sputum may be green or yellow in any case of pneumonia should limit the use of the term "jaundiced sputum" to the cases in which icterus is manifest.

At the time of crisis the sputum becomes less tenacious, more abundant and mucopurulent in character, and the pigmentation progressively fades until a white mucus is expelled. The quantity raised during the disease is small, indicating, as do metabolic investigations, that most of the exudate is absorbed and not expectorated.

Microscopically smear preparations show a field in which there are swollen red corpuscles in various stages of preservation, columnar and pavement epithelial cells, polymorphonuclear and mononuclear leukocytes and oil droplets. Pneumococci, both extracellular and intracellular, are numerous and decrease after crisis. The isolation of pneumococci in pure culture from the washed sputum in a given case is strong evidence that the organism is the causal agent of the disease.

Chemically there is an increase in protein substances, especially albumin, an increase in the fixed salts, more potassium than sodium compounds and an absence of alkaline phosphates.

Variations in Sputum.—Occasionally the sputum is not rusty but is "bloody" throughout the course. Hemorrhagic sputum is seen when pneumonia complicates or is complicated by chronic passive congestion of the lungs and in traumatic pneumonia. When it is expectorated in an apparently uncomplicated attack, the suspicion of a tuberculous origin should be aroused and pulmonary infarct should be considered.

Only in rare cases of uncomplicated lobar pneumonia is pure blood expectorated in large amounts.

Prune juice sputum, so called because of its color and fluid consistency, is occasionally raised and may indicate the onset of pulmonary edema, a severe type of the disease, the beginning of resolution, or occasionally the development of gangrene of the lung.

The expectoration of *green sputum* may have no especial significance, but it occasionally indicates an incorrect diagnosis or a developing complication. It occurs in uncomplicated pneumonia, in pneumonia with jaundice, in delayed resolution and in abscess of the lung. In no case in which it is a persistent finding ought careful repeated search for tubercle bacilli be neglected.

A very foul odor, *fluid brown sputum*, especially if it contains tissue fragments, may indicate gangrene of the lung.

In *pneumonic sputum* plugs and casts of fibrin are quite frequently found. They vary from small, rolled threads of coagulated fibrin to large, branching forms, and even perfect casts of bronchi may be expelled.

(e) *Circulatory System.*—*Cyanosis.*—Slight cyanosis is an almost constant finding in pneumonia, but intense grades do not occur in over

10 per cent of collected cases. By most observers it is usually ascribed to disturbances of respiration, but some clinicians regard it still as indicative of circulatory embarrassment and treat it accordingly. Although doubtless myocardial weakness that leads to a slowing of the circulation in the pulmonary area and to edema of the lungs with lessened diffusion of oxygen is a frequent cause for the appearance of cyanosis in pneumonia, it is important to bear in mind that disturbance of respiration is the more usual cause of deficient oxygenation, as has already been indicated (on page 18).

When cyanosis occurs early in the course of an attack it is a grave prognostic sign. It is especially marked in secondary pneumonia in individuals with emphysema or cardiac disease; in the course of complications (dilatation of the right heart, endocarditis, pericarditis, etc.); in the alcoholic and aged, and following the prolonged administration of coal-tar derivatives.

The old view that this sign is due to deficient aëration of the blood, resulting from the diminution of respiratory surface, is no longer tenable, in spite of the often noted parallel between the degree of the cyanosis and the extent of the consolidation and the observation in two cases of a diminished oxygen content of the blood with an increase of the carbon dioxide. Peabody³⁰ has shown that in most cases of uncomplicated pneumonia the decrease of respiratory surface is completely compensated and the oxygen content of the blood is within normal limits; that the blood often shows a low content of both oxygen and carbon dioxide and that in the blood of cases with marked bacteremia and of individuals who did not die with great suddenness there is, in addition, a diminished oxygen-combining capacity of the blood similar to that noted in rabbits infected with the pneumococcus and without pulmonary lesions. By experiments *in vitro* and from studies of the blood of rabbits infected with pneumococci, Butterfield and Peabody demonstrated that these changes result from the conversion of hemoglobin to methemoglobin by the direct action of the pneumococcus, and by analogy it is fair to assume that a similar process in man may account in part for the cyanosis and in some instances may explain a lethal result.

Pulse.—The normal ratio between respiration and pulse is 1:4.5, but in pneumonia this proportion may be 1:3, 1:2 or even 1:1.5.

During the chill the pulse is small, rapid and hard. After the rigor it is usually full and bounding. It remains accelerated during the course of the disease, in cases of moderate severity varying between 105 and 115, but in severe attacks in children, the aged, and when complications develop, it may be much more rapid. In the very young a rate of 200 is not uncommon, but when in an adult a tachycardia of more than 125 is met with it is a grave prognostic sign. Mackenzie states, "I have rarely seen an adult patient with a pulse over 140 recover." The rate alone, however, is not a good index for prognosis unless the other characteristics of the pulse are duly considered. The pulse rate is more rapid in women than in men, in the small than in the large. Increased frequency of the pulse at the onset is not so unfavorable as if it develops in the course of the disease.

During the course of an attack the pulse volume is usually smaller than at the onset, depending to some extent upon the lessened filling of the left ventricle; and respiratory arrhythmia is encountered fairly fre-

quently. *Diastolic murmurs*.—Often a soft pulse is indicative of a lesion of the myocardium.

Arrhythmias before crisis, as *heart block* infrequent, is regarded by Mackenzie as a very ominous sign. "In all cases of lobar pneumonia that I have met, when the pulse showed even an occasional irregularity before the crisis was reached, death supervened."

With crisis the rate decreases proportionately with the fall in temperature, and not infrequently an actual bradycardia is present during convalescence. When the myocardium has been injured when complications develop, as the neurotic and in patients with hyperthyroidism, tachycardia persists.

Blood Pressure.—The changes of blood pressure in pneumonia have been much discussed.³⁷⁻³⁹ Weigert⁴⁰ decided from a review of the literature that no conclusions concerning its variations could be established. At direct variance with this view is that of G. A. Gibson,⁴¹ who formulated what has since been known as Gibson's rule: "A pressure appreciably below the normal in pneumonia is invariably of evil omen and any considerable fall bodes disaster. When the arterial pressure, expressed in millimeters of mercury, does not fall below the pulse rate, expressed in beats per minute, the fact may be taken as of excellent augury, while the converse is equally true."

This dictum met with almost universal acceptance until the observations of Newburgh and Minot⁴² appeared, which showed that the assumption that the blood pressure is abnormally low in fatal cases of pneumonia is incorrect and, further, that the vasomotor reflexes are normal in these cases. From the results of their observations they conclude that prognostic inferences based on the relation of systolic pressure to the curve of the pulse rate are more often incorrect than correct.

From clinical experience the following statements are warranted. The blood pressure is frequently lowered during pneumonia, but there are many cases in which, throughout the entire course, a normal pressure is found. The severer cases are more apt to have hypotension than are the mild (Stachelin⁴³).

Usually the fall of pressure is not marked, though in fatal cases a drop of 70 to 80 mm. of mercury is seen sometimes. A decrease of pressure of 10-15 mm. of mercury is without significance, but a gradual progressive fall is evidence of cardiovascular weakness and an indication for treatment. An abrupt fall of pressure greater than 25 mm. of mercury is of grave portent. There is no characteristic alteration of blood pressure associated with the febrile crisis.

Heart.—To make a satisfactory prognosis and to treat lobar pneumonia efficiently, it is essential that careful and accurate observations of the condition of the heart be made from the outset.

The location of the point of maximum impulse, the determination of the right and left limits of cardiac dulness, the mapping out of the configuration of the cardiac area and of the angle between cardiac and hepatic dulness are no less important than is the accurate evaluation of the auscultatory phenomena.

Changes in percussion findings may give early clues to dilatation of the heart and beginning decompensation. Alteration in outline may discover pericardial effusion. Weakening of the pulmonic second sound may forecast myocardial insufficiency and displacement of the heart lead to the detection of a pleural exudate. Increase of cardiac dulness to the

right may result from dilatation of the right heart, from pericardial effusion, or it may be evidence of a displacement of the heart due to pleural exudation or massive pulmonary consolidation on the left side. Apparent enlargement or displacement to the right may be the result of retraction of the right lung (Jurgensen).

As already noted, the heart rate is usually accelerated and the tachycardia may be moderate or marked. After crisis bradycardia may develop. Several instances of heart block developing in the course of the disease have been described.³⁰

Cardiac arrhythmias of all types may occur, especially in patients with old myocardial disease, endocarditis or atherosclerosis. They are always of serious portent except when they are arrhythmias that have been present for years without signs of cardiac disease.

Gallop rhythm, especially the protodiastolic variety—a three-time rhythm with the third sound occurring early in diastole—is occasionally heard and usually is indicative of myocardial weakness. Tic-tac rhythm or embryocardia occurs occasionally. The pulmonic second sound is usually markedly accentuated, probably as a result of the increased resistance, and therefore augmented pressure in the lesser circulation; and occasionally it is reduplicated. A loud snapping second pulmonic sound, other things being equal, is of good augury, and when this sound becomes enfeebled it may foretell failure of the right heart and collapse. Often one fails to recognize enfeeblement of this sound because of its increased transmission through consolidated lung tissue.

Heart murmurs are of common occurrence.⁴⁴ During the active febrile stage of the disease a soft blowing apical systolic murmur is usually audible. Unassociated with cardiac enlargement and localized to the apex, transmitted over the body of the heart but not usually lateralward, and disappearing during convalescence, such a bruit is to be considered a functional murmur and not indicative of a true mitral lesion. It may result from relaxation of the heart muscle, changed composition of the blood or altered pressure in the pulmonic circulation. Of course if a preëxistent valvular lesion is present, the murmurs associated with it may be heard. Whenever murmurs appear during the course of an attack and especially if they are diastolic in time, the presence of an endocarditis should be suspected.

The development of arrhythmia, gallop rhythm, embryocardia or of cardiac dilatation may come on gradually or abruptly, but outspoken evidence of cardiac weakness is uncommon before the third or fourth day of disease. Not infrequently it is detected just before or at the time of crisis—rarely after crisis. Cyanosis, dyspnea, chilliness, sweating, delirium, increased tachycardia and hypothermia are the signs noted in cases of syncope or collapse which may be fatal or from which recovery may follow. When such signs occur the outlook is always exceedingly grave, and this is especially true if they are of postcritical development.

Sudden death may result from acute dilatation of the heart or from pulmonary embolism.

The cardiac weakness is attributed variously to myocardial injury, the direct result of the toxemia; to increased cardiac strain, the result of obstructed pulmonary circulation; to the fever; to vasomotor paresis, or to a combination of these causes.

Newburgh and Porter⁴⁵ have shown that the heart muscle in pneu-

monia is essentially normal, having adjusted itself to its poisoned food as a result of a very gradual exposure to the toxin in the blood.

(f) *Skin*.—Herpes simplex occurred in from 5 to 50 per cent of collected cases,⁴⁶ and by many is considered a favorable prognostic sign. The eruption appears most commonly on the lips or near the angle of the mouth, usually at the junction of the skin and mucous membrane; but it may develop within the nose, on the chin, ears, extremities or about the anal and genital regions. It may appear before the rigor or within the first few days of the disease, and rarely the vesicles may first erupt with beginning resolution. In some cases of herpes in the area innervated by the trigeminal nerve, Howard⁴⁷ found inflammatory and degenerative changes in the gasserian ganglion.

In an infectious disease of undetermined etiology the presence of facial, labial or nasal herpes brings into serious consideration lobar pneumonia, malarial fever, influenza and epidemic meningitis. Erythema of the face and of the skin of other parts of the body is often present during the febrile stage of the disease. Flushing of one cheek, on the same side as the pneumonia, is said to be of common occurrence.

Sweating may occur at any period of an attack, though it is uncommon except at crisis or with the development of complications. Occasionally at the height of the fever, instead of a hot, dry skin there is profuse perspiration (sudoral type). Accompanying defervescence there is usually a drenching sweat, especially marked in youthful patients. Profuse perspiration may appear in the pre-agonal stage of the disease with signs of collapse, as an accompaniment of the motor agitation of the delirious, and when empyema or other complications develop.

Miliaria crystallina and miliaria rubra develop quite often as a result of the sweating. Purpura and furunculosis are of uncommon occurrence, and a roseola-like eruption has been described. Jaundice is described under Complications (p. 47).

(g) *Gastro-intestinal Tract*.—As in most febrile diseases, gastro-intestinal symptoms occur often without active disease of the digestive organs. The tongue is usually dry and heavily furred. Sordes may be present on the lips and teeth and anorexia is present from the onset. Nausea and vomiting are relatively infrequent symptoms except in children, in alcoholics, in patients with especially violent paroxysms of cough and in those with abdominal complications. In the cases collected by Norris, nausea occurred in 13.5 per cent, vomiting in 26.8 per cent.

Hiccough may be harassing and, when it cannot be relieved, clouds the prognosis. Persistent hiccough is often indicative of a diaphragmatic pleurisy or of peritonitis.

The bowels are usually constipated, sometimes regular and occasionally there is diarrhea. The last may be due to a purgative taken at the onset or to a complicating ileocolitis.

Tympanites, or meteorism, especially common in the severe toxic cases and in those with grave circulatory disturbances, is an annoying and oftentimes an alarming symptom. All grades of abdominal distention are met with and, when an extreme degree is present, may interfere seriously with respiration. It may be due to a toxic paresis of the intestines, to enteritis, to limited mobility of the diaphragm, to derangement of the splanchnic circulation, or may be associated with a complicating peritonitis. The occurrence of abdominal pain has been considered.

The liver is often enlarged in pneumonia, but the finding of a palpable liver edge not only may result from enlargement but may be due to displacement downward caused by the pressure of hepatized lung, pleural exudate or subphrenic abscess.

As in most infectious diseases, there is some enlargement of the spleen, but it is not usually marked. The splenic dulness was increased in 90 per cent of our cases but the border was palpable in only one-third of them. When the edge is felt it is usually soft and does not present more than a few cubic centimeters below the costal margin. With the subsidence of the acute stage of the disease the splenic swelling regresses.

Lymphadenitis with enlargement of the cervical and inguinal nodes has been noted often, but in the writer's experience it is a rare finding.

(h) *Nervous System*.—Nervous prodromata are uncommon, but next to the respiratory and circulatory symptoms the nervous manifestations are the most marked.

Headache is present often at onset and subsides during the progress of the disease. Rarely severe, it may be so intense as to suggest meningitis. The pain is usually increased by, and may be excruciating during, the paroxysms of cough.

Insomnia or restless sleep may occur early in the disease and may result from pain or from frequent coughing. Somnolence at onset is a sign of graver significance, except in children. Torpor and coma occur in the very toxic cases and with meningitis.

Convulsions are rare in adults, fairly frequent in children and are not uncommon in the alcoholic, the epileptic, the insane and in individuals with a psychoneurotic tendency. von Ziemssen has described recurring convulsions in children from the onset to the termination of an attack.

Delirium is the usual manifestation of the functional involvement of the nervous system. It is outspoken especially in children,⁴⁸ in the alcoholic, in the very toxic cases, in those with meningitis, in patients with apical pneumonia and in those with hyperpyrexia. Delirium occurs in from 15 to 31 per cent of the cases. It is more commonly met with in the cases that go on to a fatal termination and in consolidation of the upper lobe. The delirium does not vary directly with the elevation of temperature.

The mental disturbances, often of abrupt onset, vary from a low muttering delirium to states of excitement, and outspoken mania has led to the admission of patients with acute pneumonia to insane asylums. There may be torpor, confusional states, disorientation—as to time, place or person—and general incoherence. Hallucinations, delusions of all varieties, paranoid ideas, etc., are not uncommon, and typical, expansive delirium with grandiose ideas occurs. During a delusional state the patient may do himself hurt or become suicidal.

Delirium tremens is often precipitated by an attack of pneumonia but is seen less often than when venesection was freely practiced. The delirium developing at the time of crisis, during crisis and posteritically, is an exhaustion psychoneurosis in contradistinction to the toxic types occurring in the course of the disease. Aufrecht has noted delirium after crisis in children and in adults who showed no nervous symptoms during the attack.

Posteritical delirium may develop immediately after crisis, with or without a marked fall of temperature, may reach its height in several

days or a week, and may leave an altered mental state that requires weeks before returning to normal. In other cases a confusional state may occur that is corrected in a few days. (These phenomena are similar to those occurring after typhoid fever.)

Meningismus and meningitis are considered under Complications (pp. 44, 45).

Physical Findings.—**DETERMINED BY INSPECTION.**—Inspection yields data of great diagnostic worth. The rapid, shallow breathing, the movement of the ala nase, contraction of the accessory muscles of respiration, dyspnea, cyanosis of skin and mucous membranes, flushed cheeks and the presence perhaps of herpes labialis or herpes nasalis all are suggestive.

The posture, too, may be helpful. When there is much thoracic pain due to accompanying pleuritis, the patient lies usually on the affected side and, by pressure with hand or pillow, aims to limit its motion. The dorsal decubitus is often assumed.

Frequently there is limited expansion on the side of the diseased lung though the immobility is not so marked as when there is pleural effusion. When the lower lobe is involved, the upper thorax on the same side often has a wider excursion than does that on the healthy side. If the right lung is affected, compensatory overexpansion is sometimes noted on the left, and *vice versa*. It is not rare to see apparent lagging of the uninvolved side, a finding that may lead to an erroneous impression if noted early, before other signs become manifest.

Limited movement of the diaphragm, as evidenced by altered Littre's sign, may be found.

The point of maximum cardiac impulse may be displaced slightly to the right if the left lung is involved, and conversely.

Mensuration of the chest with circumference or tape rarely yields any data of value. There may be increased fulness of the affected side when consolidation is outspoken.

DETERMINED BY PALPATION.—By palpation altered relative expansion of the two sides of the chest may be discovered. Early in the disease there may be a diminution of vocal fremitus over the affected lung, but more characteristic is the increased fremitus when consolidation has developed.

The vocal fremitus may be diminished if there is marked pleural thickening or if there is a very thick fibrous pleural exudate. It is diminished or absent when there is pleural effusion and in so-called massive pneumonia when the bronchi are plugged with exudate. In some cases the fremitus may return if through narrowing the bronchial secretion is dissolved or expectorated. In women and children and in all individuals with a voice that is feeble or of high pitch, determination of altered vocal fremitus is of little value. In deep-seated or central pneumonia the fremitus may be unchanged.

A palpable fremitus may be found when fibrous pleurisy is present, and rhonchal fremitus is usually palpable when there is an accompanying bronchitis and during resolution.

DETERMINED BY PERCUSSION AND AUSCULTATION.—Percussion and auscultation yield the most informing data.

(a) Percussion.—**1. Signs of Enlargement.**—The normal pulmonary resonance is replaced by a note distinctly comparable in character. There

is usually neither outspoken tympany nor outspoken dullness, but the note can be described best as a dull tympany. The cause of the hollow character of the sound is not completely established but it is likely due to diminished elasticity and relaxation of the lung, and, in part at least, to the transmission through the engorged tissue of the note from the trachea, bronchi and underlying relatively normal lung.

(ii) *Stage of Consolidation.*—The percussion note is dull. The area of dullness varies with the extent of the hepatization and is usually greater in size than is the consolidation itself. Recognition of the fact that the area of dullness may be localized and small will save errors in diagnosis, for it will lead to careful percussion of all areas of the chest. It is too common an error that, although the front and back of the chest are carefully explored, the axillary regions are often passed over unstudied. The error resulting may be maximum, for when consolidation begins in the upper lobes the dullness is often first to be detected in the posterior axillary line or at the apex of the axilla. Then, too, in women exploration of the middle lobe is often totally neglected because carelessness or mock modesty deters the examiner from raising a pendant breast. Failure to examine the entire chest thoroughly may prove embarrassing.

The note may be flat and a sense of increased resistance to the finger may suggest the presence of pleural effusion, though the absence of a board-like quality to the note and the accessory signs will save confusion. Lord⁴⁹ described the presence of a paravertebral area of relative resonance on the *affected* side in cases with extensive consolidation of a lower lobe, and this sign is often helpful in differential diagnosis.

A narrow zone of tympany at the upper level of dullness (Skoda's resonance) may be present, probably due to compression of the lung adjacent to the consolidated area. There is often a compensatory hyper-resonance of the uninvolved portions of the lungs.

In central pneumonia the percussion note is often very slightly altered, sometimes entirely unchanged, and the diagnosis rests on the data furnished by the anamnesis, by inspection and by auscultation.

(b) *Auscultation.*—Suppression of the breath sounds, partial or nearly complete, is often the first auscultatory finding in pneumonia. The discovery of diminished resonance, distant breath sounds and crepitant râles within a few hours of a rigor constitutes strong presumptive evidence of a developing consolidation.

At first, the quality of the respiratory murmur may be practically unaltered, but as solidification of the lung progresses, expiration becomes lengthened, its pitch becomes higher and soon the breath sounds become more intense and outspokenly tubular in character. At the height of the disease they are shrill and high-pitched during both inspiration and expiration. If pleural thickening is marked, if there is excessive fibrinous pleural exudation, if the bronchi are obstructed, distant tubular breathing may be present throughout the course. The altered character and intensity of the breath sounds is due to the ready transmission of the sounds in the trachea and bronchi through a solid conducting medium. The early suppression results from the incomplete infiltration of the lungs and the partial blocking of the bronchi and alveoli with increased secretion.

Of the adventitious sounds, the crepitant râle, as Laennec indicated, is the most important. He considered it "pathognomonic of inflam-

matory engorgement of the lung," and, though it is no longer so considered, it is suggestive and is met with only in early pneumonia, tuberculosis, atelectasis and infarct. Crepitant râles are very fine, crisp, metallic, consonating, dry sounds that are heard in showers toward the end of inspiration. They are only slightly altered by cough and may readily be confused with the fine râles heard in edema or congestion of the lungs, and in capillary bronchitis or with a pleural friction rub. They are produced by the inspiratory passage of air through tenacious secretion at the junction of bronchiole and alveolus in the neighborhood of consolidation.

This so-called "crepitatio indur" may come and go, and when consolidation is complete, disappears. The fine râles accompanying resolution, "crepitatio redux," are often more moist in character. The appearance of crepitation in a new area of the lung is often indicative of the spread of consolidation. During the stage of resolution moist râles of all types and musical rhonchi are heard, as the breath sounds lose their bronchial character and return to normal.

The transmission of the voice sounds is also altered. During the stage of engorgement it is often diminished, but when consolidation is complete it is increased. The spoken and whispered voice sounds are then loudly heard, more readily distinguished than over normal lung, and are high pitched and blowing in character (bronchophony). These findings are better noted in proportion as hepatization approaches the surface of the lung, and in deep-seated consolidation the intensity of the sounds is lessened but the altered qualities are still noted. The changed character and increased intensity of the voice sounds are due to the transmission through solidified lung parenchyma, which is an excellent conducting medium.

Bronchophony is more readily detected in men than in women or children, in the thin than in the obese. It may be absent in massive consolidation and is of lessened intensity or absent when there is pleural exudation. Occasionally the voice sounds have a nasal or bleating quality (egophony). The sound produced by cough also has a bronchial quality during the stage of consolidation.

The heart sounds are often transmitted loudly through the consolidated lung. In massive pneumonia other viscera may be displaced downward and towards the unaffected side.

Any or all of the foregoing signs may vary from day to day during the course of the disease, and during the stage of resolution a paroxysm of coughing may alter radically the auscultatory findings.

Resolution is usually detected first by the appearance of crepitation, the elements of which are coarser and more numerous than those of the crepitatio indur; the bronchial character of the respiratory murmur gradually becomes less well defined and with the diminishing dulness of the percussion note, coarse, moist and musical râles become more numerous, though not infrequently increasing resonance may develop without the occurrence of crepitant or coarse rhonchi. The physical manifestations of consolidation do not disappear at the crisis and it is usual that impaired resonance, distant, altered breath sounds and râles persist for days after convalescence has set in. In cases with so-called delayed resolution or with organization of the exudate, the signs of consolidation may be present for weeks or months.

The signs of consolidation may be masked or absent when there is

massive pneumonia, when there is obstruction of the bronchus, when pleural thickening or exudation is marked and in central pneumonia. When the lower lobes are the site of disease the signs are usually first detected in the back near the hilus of the lung, and when the upper lobes are involved the signs may be discovered first near the apex of the axilla.

It is important to realize that deviations from the normal findings may be noted over the uninvolved lung. In extensive consolidation of one lower lobe, tubular breathing with or without râles may be heard near the spine on the opposite side, and occasionally the percussion note may be less resonant than normal. These findings may be due in part to compensatory overaction of the unaffected lung and to altered pulmonary circulation. Ignorance of these facts may lead to diagnostic errors.

Laboratory Findings.—BLOOD.—The red corpuscles are usually normal in number during the active stage of the disease. Instances of polycythemia have been recorded and it is not uncommon to find a moderate reduction of the number of red cells. After the crisis there is nearly always a decrease of 250,000 to 500,000 erythrocytes, and occasionally a moderate red-cell anemia develops. The cyanosis and the concentration of the blood during the febrile stage of pneumonia may be responsible for an apparent increase in the number of red corpuscles or may conceal the presence of a moderate anemia. According to Emerson, nucleated red cells, both normoblasts and megaloblasts, are more commonly found in pneumonia than in other acute fevers. The hemoglobin content is generally normal during the course, but with the crisis it usually shows a reduction more marked than that of the red cells leading to the blood picture of a mild or moderate secondary anemia.

The white corpuscles are increased from the onset, and usually within a few hours of the initial chill leukocytosis is marked.⁵⁰⁻⁵² The count continues generally at a nearly constant level, with only slight increase or decrease, and does not show variations with the rise or fall of the temperature. An abrupt decrease in the number of leukocytes does not occur with defervescence at the time of the crisis, but their number falls more gradually and reaches normal from one to several days later. The diminution of the number of leukocytes may begin before, during or just after the crisis, and the continuance of a high count—especially if accompanied by a persistently high percentage of polymorphonuclear cells—suggests the presence of a complication, especially empyema or otitis media. A persistent leukocytosis with a diminishing percentage of polymorphonuclear cells and a proportional increase in the number of lymphocytes and eosinophils may indicate delayed resolution or, after serum treatment, serum sickness. In the cases with defervescence by lysis the decrease in the leukocytes is retarded.

Chatard,⁵³ in an analysis of 582 cases at the Johns Hopkins Hospital, found that more than half of the patients (350) had a leukocytosis of between 15,000 and 35,000, and nearly one-third (about 198) between 20,000 and 30,000. "The mortality is high when the leukocytes are below 10,000 per cu.mm., but steadily decreases and is lowest when the leukocytes are between 20,000 and 30,000. Between 30,000 and 60,000 the mortality is higher but remains at a fairly constant line; above 60,000, however, there is a decided rise in the mortality."

Analysis of 463 cases of pneumonia at the Hospital of the Rocke-

feller Institute and of 182 selected cases at the Minneapolis City Hospital⁵⁴ showed the same high mortality when the leukocytes were below 10,000 per cu.mm., and there was a similar progressive decrease in mortality with increasing leukocyte counts.

A leukocytosis of less than 10,000 per cu.mm. may indicate a very mild attack, a very severe infection with a poor reaction, or the presence of a complicating infection, such as typhoid or malarial fever. The lowest count seen by the writer in lobar pneumonia was 900 leukocytes per cu.mm., and in this patient anatomical examination showed, in addition to the pulmonary condition, the intestinal lesions of typhoid fever. A persistently low leukocyte count is usually an unfavorable sign.

An average leukocytosis usually indicates a good reaction, and a gradual rise of the leukocyte count during the course of pneumonia is usually a favorable sign. A leukocyte count above 40,000 per cu.mm. may be of good omen but more often indicates the development of a complication. At best, a very high count is a sign of doubtful prognostic value, for "it means that the patient is making a vigorous fight but gives no hint as to which will win, he or the infection."

The most marked leukocytic reactions are seen in males below the age of thirty and when there are complications.

(a) *Differential Count*.—The leukocytosis is generally due to a relative and an absolute increase in the number of the polymorphonuclear neutrophil cells. They average about 80 per cent of the white corpuscles, though they may constitute more than 90 per cent of them, and the lymphocytes vary inversely as the polymorphonuclear elements. The day before crisis there may be a rise in the number of cells and immature forms may appear in the circulation. During and after the crisis they diminish in number and, continuing to fall after defervescence is established, may decline to a low level. The staining reactions and the condition of the leukocytes are said to be an indication of the condition of the patient, and the predominance of degeneration forms, with poorly staining nuclei and cytoplasm, has been considered an unfavorable sign.

The eosinophils during the course of the disease are decreased or even absent, but after crisis they may rise to normal or even slightly above normal. Often myelocytes are present, especially after crisis, and may constitute as high as 12 per cent of the white cells (Emerson). The large mononuclear and transitional cells show no constant variations. The platelets are often decreased during the course of an attack but are increased after the crisis.

The leukocyte count is of considerable diagnostic aid, especially in doubtful cases. The presence of leukocytosis helps exclude an uncomplicated typhoid or malarial fever, influenza and tuberculosis (except theiliary and meningeal types), and a leukocytosis in the aged or very young, with the evidence of an infection without localizing signs, should arouse the suspicion of a developing pneumonia.

(b) *Coagulation Time*.—The coagulation time in pneumonia has been the subject of much discussion. The formerly accepted view, recently championed by Anders and Meeker,⁵⁵ that the coagulation time is shorter than normal during the active stage of the disease and returns to normal after the crisis, is no longer tenable. The observations of Doehez,⁵⁶ confirmed by Minot and Lee, definitely establish the fact that the coagulation time is prolonged before the crisis and is normal after it.

The results obtained by Anders and Meeker and by others who report like findings have been explained by the fact that they employed the old clinical method of drawing blood through a puncture of the ear or finger. When blood is obtained thus, tissue juice is added to it and accelerates coagulation. True records of coagulation time, however, can be made only when no factors of clotting are introduced; and when blood is drawn by venipuncture this condition is met. When this method is used, a shortening of the coagulation time in pneumonia is never found, though a delay may be noted, especially in very ill patients. The shortening may be due to the increased circulating fibrinogen and the delay accounted for by an increase in antithrombin. The increased fibrinogen and antithrombin content of the blood is ascribed to changes in the liver induced by the action of the pneumococcus.

(c) *Oxygen Content of the Blood.*—In uncomplicated pneumonia the oxygen content of the peripheral venous blood is within normal limits and the differences noted in the febrile and afebrile periods do not exceed those found in health (Peabody³⁶). There is no definite relation between either temperature or respiration and the oxygen content; except in the acute stage of the disease the normal oxygen level is associated with an accelerated respiratory rate. Because of tachypnea and perhaps because of a more rapid circulation, the organism compensates for the decreased respiratory surface due to pulmonary exudation. Occasionally, in uncomplicated pneumonia, a decreased oxygen content of the blood is associated with an increased carbon dioxide content, probably the result of an interference with the respiratory exchange of gases.

In the terminal stage of fatal cases, there is often a progressive diminution of the content of oxygen and of the oxygen-combining capacity of the blood. These changes develop especially in patients who have a severe sepsis and they are probably due to the formation of methemoglobin. This transformation of the hemoglobin molecule so that it can no longer take up and give off oxygen readily may be a factor in the immediate cause of death in many cases of pneumonia.³⁶

The studies of arterial blood, made possible by the method of Stadie, have shown the occurrence of severe deficiency of oxygen in pneumonia, so that instead of a normal saturation of 95 per cent, in severe pneumonia a saturation of only 75 to 80 per cent is frequently found. Symptoms of anoxemia—rapid, shallow, difficult respiration, tachycardia, delirium, asthenia, cardiac weakness, etc.—are therefore added to those of infection, and if the anoxemia is severe it may have an inimical effect on the course and the outcome of the disease.

The carbon dioxide content of the blood is regularly diminished during the febrile period. In exceptional instances it may be normal or increased and it has been found so in association with low oxygen content of the venous blood. It tends to be lowest in the very severe cases and in the terminal stages of the disease, and is less altered in the mild and abortive cases. This diminution of the carbon dioxide content of the blood parallels other manifestations of metabolic disturbances and may be most marked after defervescence.³⁷ It bears no relation to the excretion of chlorides, but corresponds to the output of ammonia in the urine.

(d) *Blood Cultures.*—Bacteriological studies of the blood in pneumonia give data of prime importance for accurate diagnosis and for

serum treatment. The earlier reports on the incidence of bacteriemia in this disease record discordant findings, but more recent evidence demonstrates that the occurrence of a blood invasion is an index of a severe infection and a grave prognostic sign. The observations of Dochez⁵⁸ in 448 cases are typical. In 136 cases with positive blood cultures the mortality was 55.8 per cent, whereas in 312 cases with negative blood cultures the death rate was 8.3 per cent.

The incidence of septicemia is higher in infections with pneumococcus Types II and III than it is in infections with Types I and IV.

The type of pneumococcus present in the circulation is a determining factor in prognosis. Statistics show that, with the exception of infections due to Type I pneumococcus, in the treatment of which specific serum is efficacious, the more virulent the type of pneumococcus obtained from the blood, the less favorable is the outlook for recovery; and the greater the number of colonies that develop from 1 c.c. of blood, the graver is the prognosis. In brief, a pneumococcus bacteriemia is always a grave condition and the gravity of its significance varies directly with the number and the virulence of the circulating organisms.

Technic of Blood Culture.—Under aseptic conditions from 15 to 20 c.c. of blood are obtained by venipuncture, usually from a vein in the antecubital fossa. The skin is most readily cleaned with tincture of iodine; the syringe is sterilized by boiling for fifteen minutes in a covered container, by heating in an autoclave or in a dry oven. A tourniquet, tightly applied proximal to the site of puncture, makes aspiration easier, and it is well to remember that oftentimes when a satisfactory vein is not visible, palpation may discover the presence of a suitable one. In the very obese it may be necessary to cut down upon a vein. When a puncture is unsuccessful, or when a hematoma is produced, it is well to withdraw the needle at once and to try another vein.

The blood obtained is immediately added to the culture media. It is the writer's practice to add 10 c.c. to a flask containing from 100 to 150 c.c. of glucose broth and to incubate it immediately. Varying amounts are added to tubes of agar melted and cooled to 45° C., and plates of the blood-agar mixture are made.

Growth in the broth is evidenced by diffuse turbidity. Growth on the blood-agar plates is shown by the development of colonies of pneumococci which appear as small dots surrounded by a green halo of methemoglobin. Organisms developing in the media are identified as pneumococci by the tests described under Bacteriology (pp. 5-10).

URINE.—The urine has the general characteristics noted in febrile diseases. It is scanty, of high color, increased specific gravity, contains a trace of albumin and often a few casts.

The output during the active period of the disease may be less than half the normal, but retention is not so common as in typhoid fever and anuria occurs only with a complicating nephritis. A postcritical diuresis is frequent. The deep color is due to increased excretion of urobilin and to concentration.

The urinary acidity, often increased during the febrile period, may be diminished after defervescence when the urine may be alkaline, perhaps due to absorption of alkali from the resolving exudate.⁵⁹ Palmer⁶⁰ has demonstrated the excretion of considerable quantities of an organic acid during the fastigium of many cases of pneumonia, and Medigreccanu,⁶¹ an increased output of glycuronic acid in the febrile period.

The urinary nitrogen is increased during resolution and more nitrogen is excreted than can be accounted for by the original quantity of exudate in the involved lung. A similar excessive excretion of nitrogen occurs in cases with delayed resolution and is evidence that this condition is one of continuing consolidation and resorption rather than one of retarded resolution.⁶²

The diazo-reaction is often present but disappears with the onset of diuresis and is of no significance.

Albuminuria is generally present before crisis and may persist into convalescence. In Chatard's ³² series albumin was present in 77.6 per cent of the cases; there was none in 16.8 per cent; a faint trace in 16.2 per cent; a trace in 68.8 per cent, and a heavy trace in 15 per cent. There was an associated cylindruria in 25.2 per cent of the cases. The albumin is usually present only as a trace. Deutero-albumose⁶³ and peptone⁶⁴ have also been demonstrated in the urine, and acetone and diacetic acid are found occasionally.

The excretion of chlorides is partially or completely suppressed more often in pneumonia than in any other febrile disease. After crisis the output rapidly returns to normal. Chatard, in a study of the urine of 103 patients, found in 50.4 per cent less than 1 gram per liter; in 31 per cent, less than 2 grams; in 12.6 per cent, less than 5 grams; in 3.8 per cent, less than 10 grams, and in 1.9 per cent, less than 15 grams. Complete suppression of chlorides is frequent.

The retention is often attributed to the storing of chlorides in the pneumonic exudate, but the experimental studies of Medigreceanu⁶⁵ and the clinical observations of Peabody⁶⁶ indicate that this is only one factor and of itself incapable of causing so marked a retention. Peabody noted that though there is a storing of chlorine, sodium and calcium, potassium and magnesium are excreted normally or in excess, that during the period of retention the chlorine content of the blood is less than normal, and concluded that "since no organ or organs have been shown to store up large quantities of the retained substances it is probable that they are spread diffusely throughout the body." That this retention is not dependent upon a renal lesion is evidenced by the normal excretion of magnesium.

The loss of nitrogen and sulfur runs more or less parallel and is less marked in mild cases.⁶⁷ The relative desamidizing capacity of the body is comparable to that in health, and the ability to oxidize the cystine group is normal or increased. During the febrile period creatinine is eliminated in excess, and during convalescence the output is less than normal. At the height of severe cases of pneumonia creatine may appear in the urine, to disappear during convalescence. In fatal cases it may be voided until death and may equal the creatinine in amount. During hyperpyrexia—especially in very toxic cases—large amounts of undetermined nitrogen may be excreted.

Dochez and Avery¹⁰ have demonstrated in the urine of patients with pneumonia a specific soluble substance that gives a precipitin reaction with antipneumococcus serum corresponding in type to the organism with which the individual is infected. This substance has been found in the urine of more than half the patients studied. It may be detected as early as twelve hours after the initial chill; it may not appear until a later stage of the disease and occasionally it is excreted after recovery has occurred. Its persistence after convalescence may

indicate delayed resolution. It is generally found when a pneumococcus sepsis exists, and the amount of precipitable substance in the urine seems to be an index of the severity of the disease. This specific precipitin test is of diagnostic and of prognostic value, and since the type of pneumococcus responsible for a given infection can be determined by its utilization, it points the way for specific therapy.

SPUTUM.—*Sputum Cultures.*—Sputum cultures are of especial value in the study of lobar pneumonia when circumstances render the taking of a culture of the blood impracticable, or when blood cultures are sterile.

The isolation of the pneumococcus from sputum offers a rapid means of identifying the strain of the organism responsible for the infection. Care should be exercised to obtain a specimen from the deeper air passages and as free as possible from saliva. It is collected in a sterile container and sent at once to the laboratory for staining, culture and inoculation into mice.

In children from whom sputum cannot be obtained in the ordinary way, a curved sterile swab inserted into the pharynx will provoke a paroxysm of coughing and the sputum that may be raised will often adhere to it, and from this cultures may be made.

DIAGNOSIS

The diagnosis of a typical case of lobar pneumonia is seldom difficult. The sudden onset of illness with a shaking rigor, fever, rapid shallow respiration and thoracic pain is suggestive. The presence of cough, tenacious rusty sputum, tachycardia, herpes and leukocytosis is corroborative evidence, and when, in addition to the foregoing, there are localized signs of pulmonary consolidation and suppression of the urinary chlorides, the diagnosis is sure. Clinically the disease has been established as lobar pneumonia, but the etiological diagnosis is not certain until the demonstration of the pneumococcus in blood cultures or sputum, or of the specific precipitable substance in the urine, has been made.

Differential Diagnosis.—But lobar pneumonia may not always present so typical a picture, and it may tax diagnostic skill to differentiate it, promptly and certainly, from other conditions. In every case of fever of doubtful origin, repeated careful examinations of the lungs are indicated. This is especially true in childhood and in old age.

ACUTE TUBERCULOUS PNEUMONIA.—Acute tuberculous pneumonia may have as abrupt an onset as lobar pneumonia, and may be characterized by all the signs already enumerated, but the history of intimate exposure to tuberculosis—especially in childhood—of an idiopathic pleurisy or of hemoptysis, chronic cough, easy fatigability and loss of weight, the presence of old tuberculous infection of the glands, etc., may suggest the correct diagnosis. When these features are lacking, an irregularly remittent or intermittent fever and failure to defervesce within the ordinarily expected time, especially when the consolidation is localized in an apex or in an upper lobe, are very suggestive. Further, in tuberculous pneumonia the constitutional symptoms are often less marked, hemoptysis is more common, the sputum less viscid and more purulent, leukocytosis less striking, cyanosis more intense and emaciation more rapid. Finally, careful and repeated examinations will often demonstrate the presence of tubercle bacilli in the sputum.

BRONCHOPNEUMONIA.—Bronchopneumonia may cause confusion when it leads to pseudolobar consolidation of the lungs; and at times differen-

tial diagnosis may be impossible. The greater frequency of lobular consolidation in infants and in the aged, its more common occurrence as a complication of or sequel to other diseases, its insidious onset, more circumscribed distribution and the greater incidence of termination by lysis are differential points.

PLEURAL EFFUSIONS.—Pleural effusions may be mistaken for lobar pneumonia, and *vice versa*. The limited expansion, the displacement of other viscera, the diminution or absence of vocal fremitus, the board-like flatness on percussion and the suppression of respiratory murmur and voice sounds, even the paravertebral triangle of dullness on the unaffected side, may be found in massive pneumonia. On the other hand, the compression of lung tissue adjacent to pleural effusions may give the signs of consolidation.

The history of a gradual onset of symptoms, the absence of a chill and of blood-stained sputum speak in favor of effusion in equivocal cases, and the demonstration of displacement of the heart to the unaffected side, of wooden flatness and Grocco's triangle on percussion, suppressed breathing and absence of râles on auscultation are points against the diagnosis of pneumonia. It cannot be too strongly emphasized that whenever doubt exists as to the presence of a pleural effusion, exploratory paracentesis of the thorax is urgently indicated. A syringe and needle suitable for thoracic tapping should be part of the equipment of every good clinician. Further, a roentgenogram gives decisive differential data.

INTERLOBAR EMPYEMA.—This condition may give all the signs of consolidation of lung tissue and may be confused with pneumonia, delayed resolution and tuberculosis. The reappearance of fever after defervescence, of sweats, chilliness, anemia, prostration and the development of clubbed fingers and leukocytosis usually point the way to a correct conclusion, or exploratory paracentesis or roentgenoscopy may discover the condition.

INFARCTION OF THE LUNG.—Infarction of the lung may closely simulate lobar pneumonia. The history may be identical and, but for the detection of conditions that may lead to embolism, differentiation may be impossible. The sudden onset of thoracic pain, cough with bloody sputum, dyspnea, cyanosis, fever, etc., point rather to infarction when they develop in patients with acute or chronic endocarditis, peripheral thrombosis, sepsis of puerperal or of other origin, sinus thrombosis, following crushing injuries, etc. In infarction, chill, rapid rise of fever and defervescence by crisis are less common than in pneumonia, and the sputum contains bright red blood and fewer bacteria. Blood and sputum cultures are helpful diagnostic aids in doubtful cases.

ATELECTASIS.—Atelectasis may present signs difficult to differentiate from those of pneumonia, though the dullness due to it is less constantly associated with intense tubular respiration; and further, the percussion changes are modified and may even approach normal, following a number of deep inspiratory efforts.

NONTUBERCULOUS BASAL INFECTIONS.—These offer little difficulty and are differentiated from lobar pneumonia by the history, mode of onset, slight constitutional symptoms, purulent sputum and protracted course.

OTHER DISEASES OF THE PLEURA AND LUNGS are rarely difficult to exclude. Tumors of the pleura, tumors and cysts of the lung and chronic

passive congestion of the lungs occasionally present signs similar to those due to pneumonic consolidation, but the history and accessory diagnostic aids will usually establish their true nature.

Central pneumonia may be overlooked for several days.

TYPHOID FEVER.—Pneumonia should rarely be confused with typhoid fever, though occasionally some difficulty may arise. The history of sudden onset with chill and thoracic pain, the presence of herpes, tachycardia, and especially of accelerated, shallow respiration, the leukocytosis and the suppression of the urinary chlorides exclude typhoid fever even before signs of consolidation of the lung develop.

INFLUENZA.—Influenza can usually be excluded by a history of exposure to contagion, by the greater prostration, green sputum, different course and by the results of laboratory investigation.

MENINGITIS.—Meningitis may be wrongly diagnosed in uncomplicated pneumonia attended at onset by marked cerebral symptoms or when there is meningismus, and examination of the spinal fluid may be the only means of differentiation. This is especially true in childhood, and in adults in whom the development of the signs of pulmonary consolidation is delayed.

ACUTE ABDOMINAL DISEASES.—Reference has been made already to the difficulties of diagnosis that may arise when acute abdominal pain is a striking feature at the onset or early in the course of pneumonia. The character of the pain, its localization, its association with rigidity of the abdominal muscles, distention of the abdomen, nausea, vomiting, fever and leukocytosis may give rise to the suspicion of peritonitis. Acute appendicitis, perforated gastric ulcer, intestinal perforation, cholecystitis, pancreatitis, even pelvic inflammatory disease may be closely simulated. Differential diagnosis rests upon careful examination of the thorax, laboratory studies and the detection of true spasm of the abdominal muscles, no less than upon an accurate knowledge of the symptoms and signs of disease of the abdominal viscera, vessels and serous lining.

X-ray Examination.—As an accessory to the ordinary methods of physical diagnosis and occasionally as the direct means of establishing the presence of a suspected but undiscovered pneumonic consolidation, the x-ray is of great value. Roentgenography is more useful than fluoroscopy in so far as it gives a permanent record and the opportunity to study the evolution of a given lesion. By means of the x-ray the exact location and extent of the inflammation can be determined and the development of effusion in the pleural sacs may be disclosed before it is of sufficient size to give diagnostic signs.

The shadow cast by pneumonic consolidation is less dense than that caused by pleural exudation or by neoplasm of the pleura or lung, and it is less uniform. As a rule, in the depth of the shadow, or more usually near its periphery, there is a diffuse, uneven mottling and the margins of the shadow are irregular, hazy and ill defined. Roentgenographic studies⁶⁸ indicate that the consolidation in lobar pneumonia begins as a conical or triangular area of solidification with its base near the pleural surface of the lung, and spreads towards the hilus. Often the infiltration does not reach the hilus and this may explain the absence of tubular breathing and bronchophony in some cases, as a central localization of the lesion may in others.

The onset of resolution can often be detected roentgenographically

before the clinical course or physical signs give evidence of its occurrence, and the x-ray has shown that resolution usually starts in the depth of the exudate, spreading irregularly from one or several points near the hilus of the lung towards the periphery. Marked changes in the shadow may occur within the course of a day, and the picture of a normal lung may not be obtained until some time after convalescence has been established.

Pleural effusion is distinguished roentgenographically from pneumonia by the following differences: The shadow is denser and more uniform; its outlines are more sharply defined and the upper limit is often curved; depression of the diaphragm, displacement of the cardiovascular stripe and a basal localization with obliteration of the complemental space are more often seen in the plates of pleural effusion.

In encapsulated exudates and when the collection is interlobar, the uniform dense shadow, its clearly demarcated borders and anatomic position are diagnostic.

The x-ray findings in thickened pleura are often confusing, but the uniform hazing without mottling and the more even paling of the shadow at its borders help to differentiate them from those in lobar pneumonia.

COMPLICATIONS

Respiratory System.—PLEURISY is so usual an occurrence in the course of lobar pneumonia that it can scarcely be termed a complication. In practically every case in which the consolidation reaches the periphery of the lung a fibrinous pleurisy develops. Occasionally the plastic exudate is of unusual thickness and extent, modifying the physical signs of the consolidation and leading subsequently to the development of adhesions. Though generally limited in area to the site of the pneumonia, it may be more extensive and occasionally occurs on the uninvolved side with resultant difficulty in diagnosis. Signs of plastic pleurisy were found in the series reported by Chatard in 51.2 per cent, but the incidence is undoubtedly greater than this figure indicates.

The presence of fibrinous pleurisy is evidenced by characteristic thoracic pain, limited mobility of the affected side and the presence of a friction rub. The last may be transitory and is readily confused with intrapulmonary crepitation. It is a point of practical importance that the sudden disappearance of pleural pain and pleural friction may indicate the accumulation of fluid as well as a subsidence of pleuritis.

Small serous effusions are of common occurrence and were found by Lord⁶⁸ in 37 per cent of 154 autopsies. Serous effusions sufficiently large to be detected clinically, *i.e.*, 400 c.c. or more, are rare.

EMPHYEMA must be looked upon as a possible complication in every case of lobar pneumonia. Musser and Norris⁷⁰ found it in 2.2 per cent of 13,550 clinical cases and in 5.1 per cent of 973 autopsies. McCrae⁷¹ found it in 3.6 per cent of 805 cases at the Johns Hopkins Hospital. The incidence of emphyema as a complication varies greatly from year to year. It is common in childhood, occurs more frequently in the negro than in the white race and is slightly more frequent in cases of pneumonia following trauma of the chest wall. The incidence of emphyema is highest in patients infected with pneumococcus Type I, next highest in those infected with Type IV and lowest in those in whom Type II is the invading microorganism.

Empyema is a complication rather than a sequel of pneumonia, as evidenced by the persistence of the fever after the pneumonia has cleared and by its occurrence during the active stage of the disease. It is more common after a severe attack and especially when more than one lobe is diseased. Its presence is usually first manifest during the stage of resolution.

The organism responsible for its production is either the pneumococcus or the *Streptococcus hamolyticus*. According to Ewart, in children empyema is due to the pneumococcus in 75 per cent and to *Streptococcus hamolyticus* in 25 per cent, whereas in adults the reverse is true.

In the series of 22 cases collected by McCrae,⁷¹ the former was found in 20, the latter in 2. In the pus of empyema cases Lord found the pneumococcus in 39.4 per cent, the streptococcus in 20.4 per cent, staphylococci in 3.6 per cent, mixed infections in 16 per cent, and in 18.2 per cent the cultures were sterile. Failure to obtain bacterial growth in cultures of the pus of empyema may indicate that the causal organism has died or that the exudate is tuberculous.

The mode of onset of empyema cannot be accurately studied, as it may be masked by the symptoms of the pneumonia. In parapneumonic empyema⁷² the only signs may be increased dulness on percussion, an increased leukocytosis and sweats. In metapneumonic empyema, which is far the more common type, the most suggestive symptom is the persistence of fever. In McCrae's series of 29 cases, in 21, after the pneumonia had subsided, the temperature did not become normal; it reached normal for a brief interval in 4 cases, remained normal for less than twenty-four hours in 2 cases, for twenty-four hours in 1 case and for three days in 1 case. The fever during the course of the empyema, though usually very irregular and often intermittent, at times may be continuous. The pulse is rapid and tachycardia may be the most striking clinical symptom. In a small percentage of the cases the rate is normal or only slightly increased.

The respirations are more constantly increased in frequency, varying between 20 and 36 per minute, are shallow and often labored.

Cyanosis may be present, but more characteristically there is progressively increasing pallor with a sallow tint to the skin. Sweats and occasionally chills, rapid loss of weight and discomfort due to pain or dyspnea are usual. Clubbing of the fingers and toes may develop rapidly.

There is an outspoken leukocytosis of the polymorphonuclear variety more marked than during the course of the pneumonia, and averaging between 20,000 and 30,000. The development or reappearance of such a leukocytosis after a critical defervescence is a very suggestive sign.

The physical signs are those of a pleural effusion. *Inspection* is of little aid in diagnosis. The limited expansion of the involved side may be interpreted as due to the pneumonic process itself, and bulging of the interspaces should not be waited for. *Palpation with auscultation* gives the most helpful data. The vocal fremitus, classically absent when there is fluid in the pleural sac, may be retained in metapneumonic empyema, perhaps due to the presence of consolidated lung tissue behind the exudate, perhaps as a result of the tension of the exudate itself. In some instances the absence of vocal fremitus may decide in favor of pleural exudation and against pulmonary consolidation. *Percussion* may show very little change from that noted during the pneumonia, but more

often the note is duller and characteristically it is flat. The complete absence of resonance due to pleural exudation is associated with a sense of wooden resistance to the pleximeter finger, so typical that it warrants exploration, even when it is the only suggestive sign of fluid. A band of kodaic tympany may be present at the upper level of flatness. Occasionally the anterior limit of altered percussion note is determined as a sharp vertical line in the axilla (encapsulated empyema). In interlobar empyema the signs may be outlined along the course of the lung fissures. *Auscultation* discloses marked changes in the breath sounds and in the transmission of the voice. The respiratory murmur may be completely suppressed or more often it may be faintly heard, usually with a distinctly tubular modification. Now and again intense tubular breath sounds may be heard when there is a large exudate in the pleural sac, a finding that may lead to an erroneous conclusion unless it is considered along with other available data. The change in the breath sounds over closely adjoining areas may be suggestive. The voice sounds are characteristically altered above the level of the fluid and generally have a curious high-pitched nasal quality that is difficult to describe (egophony).

The early recognition of an empyema is of maximum importance, for the outlook is good when a prompt diagnosis is made and efficient treatment is instituted early. Recognition of the fact that no physical sign is constantly present, and the willingness to explore the chest with an aspirating needle whenever the symptoms and some of the signs are noted, will save many a life and lead to restoration of the function of many a lung.

The prognosis of empyema is about the same as that of pneumonia itself. The earlier in the course of the pneumonia the empyema develops, the higher is the death rate due to it. This is especially true when the onset of this complication is before the tenth day of the disease. Pericarditis and endocarditis occur more often when empyema develops than in uncomplicated pneumonia.

The exudate is generally odorless, thick, creamy pus consisting mainly of polymorphonuclear leukocytes. Mononuclear and endothelial cells are present in relatively small numbers. Pneumococci living and dead may be found both intracellularly and extracellularly.

The empyema may rupture into the lung, a bronchus, the pericardium or, exceptionally, through the thoracic wall. Very rarely aspiration may be followed by absorption of the exudate, but as a rule thoracotomy with resection of one or more ribs is necessary.

The diagnosis of the rupture of empyema into a bronchus is suggested whenever, after a pneumonia, the patient suddenly expectorates a large quantity of purulent material and at the same time his symptoms lessen or disappear, the physical signs become less abnormal, the fever falls and the leukocytes diminish in number.

Encapsulated interlobar empyema may escape detection or be discovered with great difficulty. Whenever there is persistent fever, tachycardia and leukocytosis following an attack of pneumonia, especially if there are also pallor and sweats, the condition should be suspected even though physical signs do not indicate a pleural exudation. Repeated needling of the chest along the line of the interlobar fissures of the diseased side may establish the diagnosis or it may be located by the use of the x-ray (*q.v.*).

Encapsulated interlobar empyema may rupture into a bronchus and a localized pyopneumothorax may result. The writer has seen one such case in which the suspicion of its occurrence was strengthened by the demonstration of flatness that shifted along the line of the fissure with change in position.

PNEUMOTHORAX is a very rare occurrence and has been noted most often when an empyema has ruptured into a bronchus.

BRONCHITIS is extremely common at onset and may last throughout an attack. Purulent or membranous tracheitis is a rare event.

EPISTAXIS may occur as the initial symptom of pneumonia and may recur from time to time throughout the course of the disease. It is usually of no moment except in the aged or when it is a manifestation of a hemorrhagic tendency in the cases of pneumococcus septicemia.

LARYNGITIS may be present before or occur during pneumonia. Edema of the larynx and suppurative perichondritis of the larynx occur, but fortunately they are very rare.

ABSCESS OF THE LUNG is an infrequent complication. It was noted clinically in 76 of the 12,030 cases collected by Musser and Norris, and in 9 of 658 cases analyzed by McCrae at the Johns Hopkins Hospital. Lobar pneumonia is the most frequent single cause of abscess of the lung, and in 50 cases at the Massachusetts General Hospital 14 cases could be attributed to it.

There may be a single large abscess, but multiple small ones occur more commonly. The abscesses generally form near the periphery of the lung, are irregular in contour and may have a limiting membrane, though more often the boundary is indefinite and consists of necrotic tissue. The contents may be evacuated through a bronchus or the abscess may rupture into the pleura, pericardium or the esophagus.

Clinically abscess is often confused with empyema and delayed resolution. Its onset is insidious, its course not characteristic.

Irregular protracted fever, sometimes with chills, persistent leukocytosis and pallor, loss of weight, cough that is moderately productive or that may lead suddenly to the expectoration of a large quantity of purulent secretion are the classical symptoms. The cough and expectoration may be influenced much by change in posture. The physical signs are those of consolidation, and after a large quantity of sputum has been raised the signs of cavity may be detected. The sputum, first tenacious, then mucopurulent, later purulent, varies in quantity up to several hundred cubic centimeters daily. Yellow or greenish at first, it is later often blood-containing, and sometimes foul. After standing it separates into three layers. Microscopically, pus cells, detritus, epithelial cells, crystals and, more characteristically, particles or masses of lung tissue and elastic fibers are found.

After an attack of pneumonia, exacerbation of fever with leukocytosis, absence of the signs of resolution and the expectoration of large amounts of purulent sputum suggest an empyema that has ruptured into a bronchus or a pulmonary abscess. Frequently examination of the sputum will differentiate between them or recourse must be had to the x-ray.

GANGRENE OF THE LUNG is a rare sequel of pneumonia and is most common in the aged. It may begin in a pulmonary abscess or start in an old tuberculous lesion. It was found in 0.49 per cent of 27,761 cases collected by Musser and Norris and, together with pulmonary abscess,

in 0.4 per cent of 500 cases studied by Lord. Like abscess, gangrene is often overlooked clinically. The symptoms and signs closely resemble those of abscess but the constitutional symptoms are more marked and the sputum more foul. The latter is generally outspokenly fetid. It is thin, brownish, often chocolate-colored, due to altered blood. Microscopically few red corpuscles are found. Elastic tissue is less abundant and Dittrich's plugs are more abundant than in the sputum from abscess.

Gangrene of the lung may lead to the development of empyema or pyopneumothorax and to the formation of cavity. Death from abscess or gangrene of the lung may result from intoxication, suffocation, collapse or cerebral abscess.

DELAYED RESOLUTION.—The clearing of the exudate in pneumonia is brought about through a process of autolysis. Some of the exudate is removed by expectoration, but the major portion of it undergoes digestion by autolytic enzymes liberated by the leukocytes. In a variable period of time resolution is complete, and often within a week or two the physical signs of consolidation have disappeared and clinically the lung is restored to its normal state.

In some cases resolution may not proceed in this way, but its onset be delayed or its course be protracted.⁷³ Delayed resolution occurs in from 3 to 5 per cent of all cases.⁷⁴ It occurs more often in men than in women, in negroes than in whites, in pneumonia of the lower lobes, in the aged, the debilitated and in alcoholics. In the latter it may cause death from gradual or sudden cardiac failure.

Signs of consolidation may persist as long as ten or twelve weeks and yet the lung may clear.

A febrile crisis may occur and the subjective symptoms subside, but the local signs of consolidation persist, to regress very gradually over a period of days or weeks. There may be a lysis and gradual subsidence of symptoms, but consolidation of the lung associated with irregular fever and sweats may persist. Finally, the fever may remain elevated and the symptoms and signs fail to disappear, until the patient dies from exhaustion.

The condition is most often confused with pulmonary tuberculosis, interlobar empyema, pleural effusion and pulmonary abscess.

SUBPHRENIC ABSCESS is a very rare complication and deserves mention mainly because it is apt to be confused with empyema. It is probably the result of infection by direct extension through the diaphragm and not a metastatic process.

MEDIASTINITIS AND BRONCHIAL LYMPH GLANDS SUFFICIENTLY ENLARGED TO CAUSE SYMPTOMS OF PRESSURE have been described in pneumonia. Both are extremely rare happenings and of little clinical interest.

Cardiovascular System.—The cardiac complications of pneumonia are of cardinal importance, not alone because of their influence on the immediate prognosis but because of the permanent changes they may cause.

PERICARDITIS is the most frequent cardiac complication of pneumonia and occurs more often than bedside observations indicate. Collected statistics show a clinical incidence of 1.5–2.5 per cent, whereas according to postmortem studies it is found in 10 to 15 per cent of the fatal cases. It develops most commonly in young adults and is not rare in terminal pneumonia.

Pericarditis develops at the height of the disease, and because of its

insidious onset is usually not detected. Because of the frequency with which it occurs when there is consolidation of the left lung it has been thought the result of infection by direct extension; but the studies of Chatard,⁷⁵ of Sears and Larrabee,⁷⁶ and others indicate that it is generally of metastatic origin. The incidence varies with different epidemics. Usually of the fibrinous type, effusion occasionally develops, but it is rarely of sufficient size to require paracentesis. Purulent pericarditis demands prompt surgical intervention.

The diagnosis may be suggested by increasing cyanosis, dyspnea and tachycardia and is confirmed by the detection of a pericardial friction rub, or when, less often, effusion occurs, by the appearance of the signs of fluid in the pericardial sac. Recognition of a pericardial friction rub may be difficult, due to the presence of intrapulmonary sounds or of a pleuropericardial rub. It is essential to listen daily over the sternum, along the sternal margin and over the precordium in every case of pneumonia, or the presence of a pericardial rub may escape recognition.

The prognosis when pericarditis develops is exceedingly grave, in part because of the condition itself, in part because of the frequently coincident sepsis or myocarditis. The existence of the complication is so often overlooked that accurate mortality statistics are not available. Of the cases recognized clinically from 50 to 80 per cent end fatally.

ENDOCARDITIS also is undoubtedly much more frequent than clinical statistics indicate.⁷⁷⁻⁷⁹ This is illustrated by a comparison of the figures obtained from the clinical and pathological records analyzed by Musser and Norris, who noted a clinical incidence of 0.44 per cent as contrasted with the finding of anatomical lesions in 5.8 per cent. It is said to occur more often in patients over 30 years of age, more often in women than in men and especially frequently in those with preëxistent valvular disease.

In the majority of cases it is of the ulcerative type. Though the left heart is involved more often than the right, the right heart is attacked more often in pneumococcus infections than in most other varieties of endocarditis. According to Netter's figures, in 6.7 per cent of other types of endocarditis the right side of the heart is affected, whereas in 17.8 per cent of the cases of pneumococcus endocarditis it is diseased. The aortic and pulmonary valves are the ones most often involved, and whenever the former are implicated, with rare exceptions, the lesion is ulcerative.

As a rule, characteristic physical signs are lacking and the involvement of the heart is discovered first at autopsy. In some cases the subjective manifestations indicate the condition, especially when the symptoms are those of infarction. When there is infarction of the lungs, thoracic pain, bloody sputum and signs of pulmonary consolidation may be found; in infarction of the spleen, there is pain in the lower left axilla or left hypochondrium, enlargement and tenderness of the spleen; in infarction of the kidneys, lumbar pain, oliguria and hematuria may be found, and in infarction of the central nervous system there are meningitis, hemiplegia, etc.

The existence of endocarditis is to be suspected in every case of pneumococcus sepsis (*q.v.*). Its occurrence is to be considered whenever, in a prolonged attack of pneumonia, typhoidal or meningeal symptoms develop and whenever, after the temperature has fallen to normal, there is a return of an irregular fever.⁸⁰

The character of the physical signs may be diagnostic. The detection of a systolic murmur is of little help, for it occurs regularly in lobar pneumonia without endocardial involvement. The marked alteration in the character of a systolic murmur, especially when it takes on a musical quality, is suggestive. A diastolic murmur usually is indicative of endocarditis.

In most cases the fever is irregular, sometimes intermittent and associated with recurrent chills, leukocytosis, rapidly increasing secondary anemia, and oftentimes the development of transitory nodular erythema and purpura. Meningitis complicates endocarditis in over 50 per cent of the cases.

The prognosis is extremely grave. Of the cases diagnosed very few recover. If death does not occur, chronic valvular disease results.

MYOCARDITIS is not a usual complication of pneumonia, though myocardial weakness is an occurrence of varying frequency, and there is often evidence of embarrassment of the heart muscle due to the altered pressure in the pulmonary circulation or dependent upon the existent toxemia.

Permanent injury of the myocardium due to pneumonia is a very rare event.

Tachycardia and the various types of arrhythmia that may occur have been considered.

VASOMOTOR COLLAPSE.—In many instances in which death is attributed to circulatory failure, the symptoms that develop seem to indicate that the inability of the patient to maintain an adequate cardiovascular compensation is due to a deficiency in the peripheral portion of the vascular mechanism rather than to a primary insufficiency of the heart. The syndrome designated often as vasomotor collapse—low blood pressure, weak pulse, feeble aortic second sound, pallor with or without cyanosis, cold skin, profuse sweating, diminution of urinary output, a feeling of faintness and a slowing of the mental processes or even sopor—may be encountered either with or without the development of pulmonary edema. Whatever the cause of the circulatory failure, peripheral, vascular or cardiac, it is certain that it is encountered more frequently in patients with pneumococci in the circulating blood. In fact, whatever the terminal symptoms may be in pneumonia, the fatal issue is associated in a large percentage of the cases with a pneumococcus sepsis. Thus, Cecil reports that in patients in whom the cultures of the blood were sterile, death occurred in only ten per cent, whereas in patients in the cultures of whose blood pneumococci grew, death occurred in 78.3 per cent. Further, in pneumonia experimentally produced in monkeys, in every fatal case large numbers of pneumococci were found in the circulating blood.

PERIPHERAL VENOUS THROMBOSIS is uncommon in pneumonia and has been found in about 0.5 per cent of a large series of cases.⁸¹ The rarity of it is curious when one recalls how rich pneumonic blood is in the elements necessary for coagulation. It is a sequel rather than a complication, the majority of the reported cases occurring during convalescence. The veins of the lower extremities are most often involved and, as in thrombosis of the femoral veins due to other infectious diseases, the left side is affected more often than the right. It has been observed also in the veins of the upper extremities, the external jugular, the superior longitudinal sinus and the cerebral veins. Thrombosis is slightly

more common in protracted pneumonia, and in men than in women. Arteriosclerosis, feeble circulation and an altered condition of the blood are predisposing factors, but the immediate cause is probably an infective phlebitis. The symptoms do not differ from those due to thrombophlebitis of different etiology, and gangrene may result.

The prognosis differs, depending upon the vein affected. The outlook when the femoral vein is involved is good. Pulmonary thrombosis may cause sudden death.

EMBOLISM OF THE ARTERIES is very rare, but EMBOLISM OF THE ABDOMINAL AORTA, of the lenticulo-optic artery and of the popliteal artery has been described.

The emboli may be of venous or of cardiac origin.

Urinary System.—The transitory albuminuria and cylindruria of the intense febrile stage of pneumonia and their causal renal irritation are to be regarded as regular features of the disease. Frothingham's studies⁸² of a small series of cases of this type showed no impairment of renal function.

It is often difficult to distinguish between signs of no import and those indicative of true renal degeneration or inflammation. Definite nephritis, however, is rare and occurs as a complication in less than 1 per cent of the cases. It may develop at any time in the course of an attack. Acute glomerulonephritis may occur. Edema is uncommon, hemoglobinuria is exceedingly rare, but hematuria is more frequently met. Pneumonia is not a common cause of nephritis and the renal disorders due to it are usually either rapidly fatal or end in complete recovery.

Genital System.—Suppurative orchitis following pneumonia has been recorded.

Skin.—Herpes simplex, erythema and sudamina (miliaria crystallina and rubra) are among the ordinary dermal findings in pneumonia.

In the septicemic cases, purpura, erythema multiforme and erythema nodosum occur. Furunculosis may develop and erysipelas and pemphigus may be accidental occurrences. Metastatic pneumococcic dermatitis and postpneumonic symmetrical gangrene have been described. Herpes zoster is a rare complication, but the writer saw it twice in the epidemic of 1917, both times in elderly women during convalescence from a mild attack of pneumonia.

Nervous System.—The frequency and the varieties of DELIRIUM occurring in pneumonia have already been considered. Other nervous symptoms undoubtedly due to toxemia and not dependent upon anatomical lesions may occur.⁸³ COMA and STUPOR sometimes associated with vomiting, HEADACHE and SIGNS OF MENINGEAL IRRITATION are unfavorable symptoms that may appear without the development of a true meningitis in children, in alcoholics, in very toxic cases and in association with otitis media.

PSYCHOMOTOR AGITATION in the neurotic or in very toxic cases may lead to such physical activity as to embarrass an already laboring heart.

MENINGITIS occurs in less than one per cent of all cases of pneumonia. It is most frequent in children under ten years of age and is almost uniformly fatal.⁸⁴ Meningeal symptoms may precede the signs of pneumonia or they may develop after the signs of pneumonia have subsided.⁸⁵ The infection of the meninges may be hematogenous, otogenous, lymphogenous or perhaps by direct extension from the parana-

sal sinuses. Probably in the majority of cases it is a metastatic infection of hematogenous origin, and its development in only a small group of those with bacteremia may be due to the existence in these of altered conditions of the thecal circulation. Anatomically the lesion is a purulent meningitis, indistinguishable from that due to the meningococcus or the influenza bacillus with the exudate widely distributed over the brain and spinal cord.

The symptoms may be completely masked by the toxic nervous symptoms of pneumonia and may be completely simulated by those of meningismus. Headache, photophobia, vomiting and constipation are suggestive. Stiffness of the neck, retraction of the head and Kernig's sign are even more so, and the occurrence of paresis or paralysis of the cranial nerves, convulsions, opisthotonos, emprosthotonos, hyperesthesia, choked disk, Kernig's, Babinski's and Brudzinski's signs, is practically diagnostic. The conclusive evidence of meningitis is furnished by lumbar puncture. The spinal fluid obtained is turbid or purulent. It is often under increased pressure, shows an increased content of protein, contains many leukocytes—chiefly of the polymorphonuclear variety—and many pneumococci. Purulent meningitis may develop weeks after recovery from pneumonia.

It is important to recall that though many of the foregoing symptoms may be present and the clinical syndrome be indistinguishable from meningitis, spinal puncture may show a normal fluid or autopsy may show no anatomical changes in the central nervous system. This condition is termed *meningismus*. It occurs in the very toxic pneumonias, especially in the neurotic and in children, and is of no prognostic moment.

MENINGO-ENCEPHALITIS with signs of localized or focal cerebral disease has been reported.⁸⁶⁻⁸⁷ The condition is of very rare occurrence, has a bad prognosis and is manifested by the signs of increased intracranial pressure and the development of hemiplegia or monoplegia, or by disturbances of the cranial nerves. The pathology of this complication is not thoroughly established. Tetany, transitory loss of the pupillary light reflex⁸⁸ and temporary diminution or loss of the knee-jerk have been seen during the course of the disease.

PERIPHERAL NEURITIS, PARESIS OR PARALYSIS OF THE VARIOUS CRANIAL NERVES have been noted during pneumonia or in the convalescence from an attack. These symptoms are of toxic origin and recovery from them without residual symptoms is the rule. They have no influence on the general prognosis.

HEMIPLEGIA⁸⁹ is a rare complication that may result from cerebral thrombosis, embolism or abscess. There is another type of pneumonic hemiplegia occurring in young, vigorous people and having a better prognosis. This type, without gross anatomic lesion, appears within the first few days of the pneumonia or may precede it, and often before the development of paralysis there are ataxia, aphasia, headache, syncope, vertigo, mental confusion and paresthesia of the side later paralyzed. This type of hemiplegia is of uncertain etiology and is variously ascribed to hysteria, encephalitis, meningitis and to cerebral ischemia due to insufficient circulation.

Organs of Special Sense.—OCULAR COMPLICATIONS are rarely seen. Instances of conjunctivitis, ulcerative keratitis and abscess of the cor-

nea occur, and panophthalmitis and hemorrhagic retinitis of embolic origin have been described.

OTITIS MEDIA is most often met with in childhood. It occurs in about 3 per cent of the cases of pneumonia of children and in less than 1 per cent of those occurring in adults. The ear may become infected by extension from the throat or nasopharynx or through the blood stream. The process generally leads to suppuration and the symptoms generally are those of a purulent otitis media. Occasionally the clinical picture closely simulates a meningitis. Mastoiditis, sinus thrombosis or meningitis may follow by extension. If paracentesis is not done, perforation of the tympanic membrane results, often with a consequent chronic discharging otitis, but the hearing is rarely impaired. The possible evil consequences of middle-ear disease can usually be avoided by frequent careful examinations of the ear in all pneumonic children and in all patients with signs of meningitis or with symptoms of otitis.

Thrombosis of the cerebral sinuses is to be suspected whenever, during or after an otitis media, cultures of the blood previously negative yield pneumococci (Libman and Celler⁹⁰).

Muscular System.—ARTHRITIS⁹¹⁻⁹⁴ is a very unusual complication, developing in less than 0.5 per cent of the cases. It may occur at any stage of the disease, most often in the second week and, like other manifestations of sepsis, it occurs most often in children. Mono-articular or poly-articular, it shows a tendency to involve the large joints, especially the knees, and there may be synovitis or bursitis independent of or associated with the arthritis.

Mild cases with joint pain, tenderness, redness and slight swelling are probably often overlooked and subside spontaneously. Cases with moderate serous effusions occur with little constitutional disturbance. More severe cases suffer severe arthralgia, show marked signs of arthritis and develop purulent exudate with destruction of the joint and marked general symptoms. This group associated with sepsis is often fatal, even when treated surgically.

Gastro-intestinal System.—Pneumococcus infections of the mouth are medical curiosities.⁹⁵ A case of severe pneumococcus infection with GLOSSITIS was reported in 1903 and at that time was the second recorded instance of the condition.⁹⁶

ACUTE PAROTITIS^{97, 98} is rare and may develop at any time during the course or convalescence of pneumonia. The involvement of the parotid is generally unilateral, though occasionally both glands are affected. The infection may be hematogenous but probably more often is due to direct extension by way of Stenson's duct. The symptoms are fever, often chills, dry mouth and local pain, redness and swelling of the gland. These may subside spontaneously, or suppuration may follow with drainage of pus or rupture into the mouth. It may lead to facial paralysis, otitis, necrosis of the jaw and temporomaxillary joint, to jugular thrombosis and sepsis.

VOMITING with or without nausea may be a prodromal symptom, may attend the onset of the active disease or develop during the course of an attack. It is met with most often in children, in toxic cases, as a symptom of meningitis, as a consequence of medication, and in patients with gastro-intestinal or peritoneal inflammation. Pneumococcus gastritis, gastric and duodenal ulceration,⁹⁹ enteritis and colitis rarely occur. Intestinal hemorrhages as a result of ulcerative lesions in the bowel

have been described. Appendicitis may develop during the active disease or in convalescence.

ACUTE DILATATION OF THE STOMACH is an unusual and serious complication that generally escapes detection. The stomach may be tremendously distended and may even fill the entire abdomen. According to Fussell,¹⁰⁰ the dilatation is probably due to toxemia with resultant constriction of the duodenum and a secondary obstructive increase of the dilatation. The symptoms are vomiting, abdominal pain, distention, constipation, collapse, splashing sounds and visible gastric peristalsis. Untreated, the mortality is over 50 per cent, but when frequent lavage is practiced the prognosis is generally good.

METEORISM, often present in moderate degree, may become so marked as to be a serious complication, for when abdominal distention is great, serious interference with respiration may result. It occurs in very toxic cases, with sepsis, enteritis and peritonitis.

HICCOUGH is rarely sufficiently persistent and frequent to cloud the prognosis.

PERITONITIS is one of the very serious complications. Fortunately it is rare and does not develop in more than 0.5 per cent of the cases. It may be primary or secondary, general or local. The primary localized form is most common in children and is diagnosed by the association of high fever with a tender abdominal mass and diarrhea. The secondary diffuse form is a metastatic manifestation of sepsis and develops during the same stage of the disease as pericarditis and empyema. The symptoms are those of peritonitis of other origin and whenever, with fever and leukocytosis, hiccough and vomiting are present with abdominal pain, rigidity, muscle spasm and tenderness, the diagnosis is clear. Abdominal pain and rigidity associated with pleurisy may lead to an incorrect diagnosis, but the latter symptoms usually appear early and disappear within a few days of the onset of pneumonia, whereas the symptoms resultant from a true peritonitis do not generally appear until the height of an attack. Moreover, true muscle spasm and persistent vomiting are helpful differential guides. It is especially important that in every patient with the symptoms of acute intra-abdominal inflammation a careful examination of the lungs be made, if the embarrassment of an unnecessary laparotomy in pneumonia is to be avoided.

JAUNDICE develops occasionally during the course of pneumonia and is said to occur in from 2 to 11.5 per cent of the cases. Statistics probably fail to convey an accurate idea of its frequency, as the very mild grades are often undetected.

The incidence varies in different epidemics, and the degree of jaundice that develops shades from a subicteric tinting of the scleræ to outspoken yellow or rarely greenish staining of the skin and visible mucous membranes. It is usually first apparent at the height of the disease and is more common in the toxic cases. The stools generally contain bile, but instances of catarrhal obstruction of the bile ducts with acholic feces are recorded. The mortality of the cases with jaundice is higher than in uncomplicated pneumonia and is generally placed above 50 per cent. Probably the higher death rate is due, not to the complication itself, but to the conditions that caused it.

The actual causation of the jaundice is not established. Banti¹⁰¹ regarded it as the result of a specific hemolytic action of the pneumococcus upon the erythrocytes, and his experimental observations lend

support to that idea. McPhedran¹⁰² noted an increased corpuscular resistance of the red cells in the cases with most marked jaundice, bilirubin in the urine of jaundiced patients and a destruction of red corpuscles that he regarded as due to the pulmonary hepatization.

The view that it results from an infective cholangitis finds support in the occasional development of cholecystitis, but in McPhedran's cases autopsy showed no special changes in the liver. The idea that chronic passive congestion of the liver is the causal factor is negated by the absence of signs of cardiac embarrassment and venous stasis.

INVOLVEMENT OF THE GLANDS OF INTERNAL SECRETION is very rare, but reports of thyroiditis, abscess of the thyroid gland and of purulent infection of the testicles appear in the literature.

PNEUMONIA IN ASSOCIATION WITH OTHER DISEASES

Infectious Diseases.—**INFLUENZA.**—Influenza may be complicated by the development of lobar or bronchopneumonia, and the pneumonic process may be but another manifestation of infection with the primary invader or the result of secondary infection with the pneumococcus, streptococcus or some other microorganism. Mixed infections are not uncommon. It is still a moot point as to how frequently the pulmonary consolidation is due to the *Diplococcus pneumoniae*, but it is established that when the lesion in the lungs is truly lobar it is frequently due to that agent. The influenza bacillus has never been shown to be the etiological agent in lobar pneumonia. The course of pneumonia complicating influenza is modified in that there is less often a chill at the onset, the fever is more irregular and often declines by lysis, the prostration and cyanosis are more marked, the pulse is slower, the sputum less often rusty, more often hemorrhagic, and there is usually a leukopenia. The mortality is very great. Edema of the lungs develops in a large per cent of the patients.

MALARIAL FEVER.—In malarial fever pneumonia may develop as a complication and it is practically always due to the pneumococcus. When it does occur, the prognosis is grave, the mortality high and the course is often characterized by obscure physical signs, by prostration and by cerebral symptoms. Pulmonary congestion may be a source of confusion, and it is differentiated by its basal localization and intermittent fever. Pneumonia is never due to the malarial parasite.

TYPHOID FEVER.—Pneumonia is an uncommon occurrence in typhoid fever and when it develops is more often lobular than lobar in type. Generally due to infection with the pneumococcus, apparently authentic instances of pneumonic consolidation due to the *Bacillus typhosus* have been recorded.

The pneumonia rarely occurs early in the course of typhoid fever, and when it does, its symptoms are characteristic and the existence of the latter may be first suspected because of the absence of leukocytosis, the protracted fever, the appearance of the roseola at the end of the first week; or the result of blood cultures may establish its presence. The onset of pneumonia is most frequent after the second week of the disease and it may not be detected. The pathognomonic features are often lacking and the presence of the complication may be indicated only by the accelerated respiration, cyanosis, tachycardia and leukocytosis. The last may be relative to the preëxistent leukopenia and not absolute. Cough and expectoration may be entirely absent. The mor-

tality in this group is unusually high. Finally, pneumonia may develop during convalescence and when it does there is seldom any diagnostic difficulty.

Occasionally the signs of pulmonary infarction are wrongly interpreted as indicative of pneumonia, and this is true especially when the signs of peripheral thrombosis are not evident or do not appear until after the lesion in the lung has become manifest.

MEASLES.—Measles is rarely complicated by the development of lobar pneumonia, but bronchopneumonia frequently occurs during convalescence. The pulmonary complications and sequelæ have been studied in our army cantonments and it has been demonstrated that postmeasles bronchopneumonia is usually due to the *Streptococcus hamolyticus*, and occurs most often in individuals who harbor that organism in their throats.

SCARLET FEVER; DIPHTHERIA.—Lobar pneumonia is very unusual as a complication of the other acute exanthemata and in scarlet fever is a very grave event, especially when there is a coexistent nephritis. In diphtheria pneumococcus pneumonia happens even more rarely.

PULMONARY TUBERCULOSIS.—In the course of pulmonary tuberculosis pneumococcus pneumonia is a rarity, and when it develops, differential diagnosis is extremely difficult. Subacute and acute tuberculous consolidation present the same signs and often are attended by the same symptoms as pneumococcus pneumonia, though generally the history and the course of the disease are different. Exposure to infection, especially in childhood, evidences of tuberculous lesions in the lungs or elsewhere, a previous attack of idiopathic pleurisy—especially if attended by effusion—poor general health and frank hemoptysis are helpful differential points. Further, defervescence by lysis and low-grade leukocytosis with evidence of apical disease also speak for tuberculosis. The demonstration of tubercle bacilli in the sputum is conclusive evidence of the nature of the infection. Lobar pneumonia may lead to a flare-up of an inactive lesion or may be followed by a generalized dissemination of the tuberculosis, though probably in many cases the further course of the old disease is uninfluenced.

Non-infectious Diseases.—**DIABETES.**—When lobar pneumonia occurs in this disease it usually runs an atypical course and has a grave prognosis.¹⁰³ During the course of the infection glycosuria may be lessened or even disappear, but the danger of gangrene is increased and the patients usually die in coma.

CARDIAC AND RENAL DISEASE.—In this group of cases bronchopneumonia is more frequent than the lobar variety. When the latter does occur, it may be confused with pulmonary congestion or infarction in cases with cardiac decompensation, and may be overlooked. The course of pneumonia in these diseases is very atypical, with insidious onset, slight pyrexia and abundant frothy sputum. The mortality is high.

ALCOHOLISM.—In those addicted to the use of alcohol pneumonia occurs frequently and is a very fatal disease. It has an insidious onset, an afebrile or slightly febrile course, marked nervous symptoms and generally atypical manifestations. Delirium tremens is precipitated often early or at the height of the pneumonia.

HEAT STROKE.—Heat stroke may be complicated by pneumonia and when it is the outlook is very grave, as over 50 per cent have a lethal termination.

INSANITY.—In the insane the symptoms are often very atypical and the disease may be readily overlooked.

CLINICAL VARIETIES—TYPES

The manifestations of lobar pneumonia are protean, and in addition to the classical entity, a number of clinical variants from it have been described. Such syndromes have been especially numerous subsequent to the pandemic of influenza in 1917 and 1918, since when many cases of lobar pneumonia have been seen, the manifestations of which were extremely atypical. Although the symptomatology varied little from the usual, the physical signs were so often those of a bronchopneumonic consolidation that spread so as to become lobar in extent that it was not possible always, even with a careful correlation of the anatomical changes, the clinical history and the bacteriological findings, to state whether the syndrome should be designated lobar pneumonia or confluent bronchopneumonia. Such variants from the more stereotyped picture have been encountered less frequently during the last few years.

Central Pneumonia.—When the consolidation begins in the depth of the lung, or at the hilum, and no part of the periphery is involved, the condition is termed latent or "central pneumonia." The former is the more suitable name, for often the condition is overlooked or, as the signs of consolidation may be lacking, the condition is only suspected from the history, the rusty sputum, accelerated respiration, fever and leukocytosis. Diagnosis in such cases is sometimes established by the x-ray. When the area of consolidation is in contact with patent bronchi or approaches the surface of the lung, diagnostic signs become manifest.

Massive Pneumonia.—Massive pneumonia is the term applied to consolidation of the lung with associated plugging of the bronchi. The physical signs are often those of pleural effusion, from which it may be differentiated by the appearance of the signs of consolidation following cough, the absence of Grocco's sign, the presence of resonance adjacent to the spine on the affected side, and often by the absence of displacement of the heart or other viscera. Occasionally the signs are so equivocal that exploratory thoracentesis or a roentgenogram is necessary to exclude a pleural exudate.

Apical Pneumonia.—Apical pneumonia is considered by some an especial type of the disease, characterized by delirium, often indistinguishable from mania à potu, by stupor and by hyperpyrexia. It is more common at the extremes of life, involves the right lung more often than the left, and pericarditis is said to occur more often as a complication than in other types of pneumonia. It is questionable, however, if there is any justification in setting apart pneumonia involving the apices as a clinical variety.

The mortality of the foregoing three types is essentially the same as that of ordinary lobar pneumonia.

Migratory Pneumonia.—Migratory pneumonia is an uncommon variety of lobar pneumonia in which different lobes or portions of lobes of the lungs are involved in succession. As resolution is established in one area, consolidation begins in another, the process spreading in contiguous portions of the lung. Several lobes may be involved and the disease run a protracted course. Oftentimes when the consolidation spreads

to the previously healthy side, a more marked exacerbation of symptoms occurs than when the progression is on the same side.

Short Term, or Abortive, Pneumonia.—This form is occasionally seen.¹⁰⁴ The onset of the disease may be typical, the signs of consolidation of a lobe complete, and crisis with subsidence of symptoms begin on the first, second or third day. The most striking instances of "one-day pneumonia" seen by the writer occurred in two young men, room-mates, the second of whom contracted the disease apparently by direct contagion while nursing the first. In each the disease was of sudden onset, with chill, fever and pleural pain; each developed signs of complete consolidation of the right lower lobe, and in one the crisis occurred within 22 hours, in the other within 36 hours, of the beginning of symptoms.

Senile, or Asthenic, Pneumonia.—Pneumonia in the aged or in individuals debilitated by chronic disease is characterized by the absence of prodromata, an insidious onset, severe prostration, absence of cough and expectoration, and often by the presence of coma, stupor or delirium, and by gastro-intestinal symptoms, especially nausea, vomiting and diarrhea.¹⁰⁵ The last symptoms may be so striking as to dominate the clinical picture and lead to carelessness in examination of the chest. The only symptom in many cases is accelerated respiration, or dyspnea, and fever may be absent throughout the course of the illness. The absence of other symptoms and the fact that physical signs of consolidation may be lacking for several days explain the frequency with which the existence of pneumonia is overlooked in many of these patients. Occasionally typhoid fever is suspected but it can be readily excluded. The course is usually protracted. If there is fever, defervescence is generally by lysis. Gangrene and abscess of the lung are frequent complications. The mortality is high.

Terminal, or Terminating, Pneumonia.—Terminal, more aptly termed terminating, pneumonia often presents the same characteristics as does the so-called asthenic type. Most usually met with in the aged, in the alcoholic and in patients with chronic diseases, it is not uncommonly first recognized at autopsy. An afebrile course, without cough or dyspnea, and with slight constitutional symptoms, is not uncommon. Bronchopneumonia is more common as a terminal pulmonary complication than is the lobar variety.

Pneumonia in Infancy and Childhood.¹⁰⁶⁻¹¹²—Though of less frequent occurrence than bronchopneumonia, lobar pneumonia is by no means uncommon in very early life. Holt states that after the age of three years all primary pneumonia is of the lobar variety and, according to Dunlap's statistics, it is met with as often in infancy as in later childhood. Many instances of antenatal pneumonia are recorded (MacDonald).

The disease is more common in boys than in girls. The mortality in infants is high (20-35 per cent) and in children above the age of three years is low (2-10 per cent). The duration is usually shorter than in adults, averaging seven days, and abortive pneumonia is not infrequently seen. The temperature is likely to be higher and more irregular than in adults, defervescence by lysis is more usual, and pseudocrices are less common. Hyperpyrexia is not necessarily a grave prognostic sign in children. Chill at onset does not often occur; delirium and convul-

sions are frequently the initial symptoms, but vomiting and other gastrointestinal symptoms usher in the disease perhaps even more generally.

Very important for diagnosis is the altered pulse-respiration ratio from 4:1 to 3:1, or in infants even 2:1. The character of the respirations is considered by some to be pathognomonic—inspiration, pause, expiration, grunt—this modification occurring with tachypnea of 50 to 100 respirations per minute. The child is listless and fretful and infants often are disinclined to nurse. Erythematata are often seen; herpes is rare.

The physical signs may be indefinite or even absent during the early days of the disease and may not appear until the time of or even after the crisis (Freeman).

Tympany on percussion and suppression of breath sounds are early signs, and these may be first elicited high in the axilla. Often râles and dullness appear first, late in the course of the disease.

The explanation of the paucity of early signs, their appearance in the axilla and, in some instances, failure to detect their presence at all has been furnished by roentgenographic studies. These show that the pneumonic process always begins at the surface of the lung as a triangular wedge with the base at the periphery. Signs may be lacking at first, owing to the small size of the lesion, to the fact that it does not reach a large bronchus or to its location high in the axilla or behind the scapula, shoulder-joint or at the base of the lung.

The physical signs usually clear rapidly at the time of lysis or crisis and the persistence of them often is indicative of complications.

Pain referred to the abdomen is more frequent than in adults. Rigidity of the upper extremities and neck is often due to soreness of the chest.

Cough may be a valuable diagnostic symptom when the physical signs are obscure.

Meningismus is very frequently noted, but meningitis, though a more common complication than in adults, does not develop in a large percentage of the cases. Absence or diminution of the knee-jerk speaks against the existence of true meningitis. Otitis media and empyema are the most usual complications.

In children lobar pneumonia may be indistinguishable from bronchopneumonia. The disease may be overlooked if it is not remembered that cough may be slight or absent, that the sputum is swallowed and that the physical signs of consolidation may be so obscure as to escape any but the most painstaking examination.

Postoperative Pneumonia.—Pneumonia develops very occasionally following operations, whether performed under general or local anesthesia. In most instances it is of the lobular variety, but rarely a lobar pneumonia occurs postoperatively and the mode of its production is still moot. Exposure and chilling during the operative procedures, antecedent infection of the mouth and upper respiratory tract, bronchitis, acute or chronic, may be predisposing factors. The presence of virulent pneumococci in the buccal, nasal or pharyngeal cavities, *i.e.*, a carrier state, may be responsible in occasional instances; and when general anesthesia is induced with ether or chloroform the irritating action of the vapor may open the way for infection. In many cases the disease results from aërogenous infection through aspirated mucus or saliva, though it may rarely be of hematogenous, lymphogenous or embolic origin.

Pasteur has described a condition of extensive collapse of the lung resulting from paresis or paralysis of the diaphragm, and this condition may precede the onset of pneumonia or may be confused with it in the absence of consolidation. It involves the lower lobes most often, and when it occurs suddenly, may be fatal.

Postoperative pneumonia is more common in the aged, the debilitated and after operations on the stomach, mouth, the respiratory tract and after gynecological operations.

The condition is rare, as shown by the statistics of Musser and Norris,¹¹³ according to which it occurred in 0.35 per cent of 139,101 collected cases.

Abscess of the lung is the most frequent complication.

Pneumonia in Pregnancy.—Pneumonia is a relatively infrequent complication of pregnancy, occurring in less than 1 per cent of collected cases, but when it develops it materially increases maternal mortality and often leads to premature labor or abortion. Musser and Norris state that "if abortion does not occur in the first few days the prognosis is better" and that "the third day is the most common one on which abortion occurs."

Abortion or premature labor occurs in more than half the cases, and when it does the maternal mortality is increased, due in part at least to the cardiac exertion incident to it. The frequency of abortion and the maternal death rate increase directly with the duration of the pregnancy, and even when gestation is seven months or more advanced the infant mortality is high. Death of the mother may be due to sepsis, toxemia or severe cardiac strain.

The cause of the spontaneous emptying of the uterus may be toxic or may be the result of an embolic pneumococcal endometritis. Experimental evidence for the latter origin is furnished by the experiments of Aufrecht on pregnant rabbits.

Pneumonia is less common in pregnancy than are pulmonary embolism and infarction and it may be readily confused with them (*see* Diagnosis).

Traumatic Pneumonia.—Pneumonia following injuries of the chest wall has been described,¹¹⁴ but it is of very infrequent occurrence. It may develop in individuals in whom the lung itself has not been penetrated and may follow crushing wounds. The mechanism of its causation is not established and it is still a question as to whether or not a frank pneumonia due to the pneumococcus follows trauma, though a number of apparently authenticated instances are described in the literature.

Pneumonia Following Immersion in Water.—Pneumonia due to this cause occurs occasionally and is generally of the lobular variety. True lobar pneumonia may develop. Etiologically chilling and shock are of some importance. It is probable that in this group of cases the presence of pneumococci in the buccal cavity and upper respiratory tract is the direct determinant of whether or not aspiration of water will lead to pulmonary consolidation.

Typhoid Pneumonia.—This ambiguous, undesirable term should be abolished from our nomenclature. It is rarely clear whether it refers to pulmonary consolidation, the result of infection with the *Bacillus typhosus*, or to true pneumococcus pneumonia with symptoms resembling

those of typhoid fever. Both conditions occur, though pneumonia due to the typhoid bacillus is a very rare disease.

Secondary Pneumonia.—Secondary pneumonia has already been considered under the caption of Pneumonia in Association with Other Diseases and, as has been stated, its signs and symptoms often deviate markedly from those that are met with in uncomplicated frank pneumonia.

Whenever in the course of any disease there is noticeable disturbance of the normal respiration-pulse ratio, the existence of pneumonia should be suspected. Even careful physical examination may then fail to disclose the signs of consolidation and the diagnosis must be made from the symptoms, the fever and the character of the respiration. Unless an investigation of all parts of the lungs is made, including the axillæ, the middle lobe, the regions covered by the scapulæ and the supra-clavicular and infraclavicular regions, errors will be frequent. Oftentimes there is great difficulty in deciding whether the lesion is a bronchopneumonia, atelectasis, hypostatic congestion, pulmonary infarction, edema or a central pneumonia.

Organizing Pneumonia.—In rare instances the exudate, instead of undergoing resolution and resorption, becomes organized, leading to fibrosis of the lung. This occurs most often in cases of delayed resolution and leads to permanent impairment of the function of the affected area.

TREATMENT

Prophylaxis.—The failure to eradicate or to lessen the incidence of pneumonia has been due in part at least to the failure to recognize its usual mode of dissemination. Though it is perhaps true that in some cases the disease may arise from an auto-inoculation with pathogenic strains harbored in the mouth, the studies from the Hospital of the Rockefeller Institute have apparently established the fact that most often it is the result of infection from without due to contact, direct or indirect.

This statement is true of infections with Types I and II, which are responsible for over 60 per cent of all pneumococcus pneumonias studied. These strains are very rarely present in the mouths of normal persons who have not been in intimate contact with patients and they persist for only a limited time in the buccal secretions of convalescents from the disease. Pneumococci are found in dust, but pathogenic types are never found except in the environs of patients ill with pneumonia or in the quarters of healthy carriers. The chief sources for the spread of pneumonia are patients with pneumonia, convalescents who harbor the organisms in their buccal secretions ("convalescent carriers"), persons who have acquired the organisms by intimate contact with patients ("healthy carriers") and dust from the immediate surroundings of patients or carriers. Recognition of these facts in regard to the dissemination of pneumonia due to Types I and II pneumococcus, and the realization that auto-inoculation with a pathogenic strain present in the mouth may rarely occur, furnish a basis for the prophylactic measures to be taken.

GENERAL MEASURES.—To prevent the spread of pneumonia the same general measures are needed as are helpful in lessening the dissemination of other infectious diseases. The public must be educated, ade-

quate legislation must be had and a well equipped board of health is necessary properly to enforce enacted laws. The compulsory reporting of each case of pneumonia will furnish new and important data concerning the epidemiology of the disease, and the employment of laboratory procedures will offer wider opportunities for the use of specific treatment.

Each case of pneumonia is a possible focus for the spread of infection, and the measures of isolation helpful in controlling the dissemination of other contagious diseases should be instituted. Inasmuch as the buccal and **respiratory secretions** are the chief sources of contagion, they should be carefully collected and burned or disinfected. A 5 per cent solution of **carbolic acid** or of **lysol** is useful for this purpose. Before removal from the room, handkerchiefs, bed and body linen, clothing, utensils, etc., should be **sterilized** by boiling or by the use of disinfectants. Thermometers and all other appurtenances of the sick-room should be kept separate from those used for other patients.

Since it has been shown that the environs of the patients are contaminated, **daily cleansing of the room** should be carried out in such a way as to avoid scattering of dust, and after convalescence the room should be thoroughly cleansed and aired. Hot soda water is an admirable cleanser and **sunlight and fresh air** are more valuable than fumigation.

Attendants of the patient are best protected by good habits of **personal hygiene** and by scrupulous care of the mouth and nose through the use of ordinary so-called antiseptic mouth washes. Kolmer and Steinfield¹¹⁵ recommend as especially efficacious the following solution:

Ethylhydrocupreine hydrochloride or quinine bisulfate, 0.005 gram.

Liquor thymolis, 5 c.c.

Distilled water, sufficient to make 50 c.c.

The wearing of a **gauze mouth and nose guard** likewise lessens the danger of infection.

The control of carriers, convalescent and healthy, is more difficult, for it is not practicable to isolate all those who harbor the organism. All known carriers of pathogenic types of pneumococci should be instructed as to their potential harmfulness and cautioned to **avoid coughing and sneezing** without shielding the mouth, and to avoid **expectorating** except into proper containers, and in the use of **mouth washes** which may be helpful in ridding them of the cocci.

Finally, individual cleanliness, in its broadest sense; recognition of the value of fresh air and sunshine and of the dangers of poor ventilation and improper housing; avoidance of excess and of exposure, especially when fatigued or when "suffering with a common cold," and observance of all the rules of good hygiene are invaluable preventive measures.

SPECIFIC MEASURES.—Vaccination.—Though a rational basis for prophylactic vaccination against the pneumococcus has been established, attempts to carry out this procedure successfully have generally failed. These unsuccessful efforts in the past were undoubtedly due to a failure to recognize or to consider the different immunologic groups of the pneumococcus.

The earliest important studies along this line were those of Lis-

ter,¹¹⁶ who studied the effects of vaccination among the mine workers at Kimberley, South Africa. He injected a large group of men with a triple vaccine made of the three types of pneumococcus that had been found responsible for the cases of pneumonia among the workers, and noted a markedly diminished incidence of subsequent infection among them, as contrasted with that occurring among the unvaccinated. Lister utilized cultures that were killed by the action of a germicide and administered three subcutaneous injections at seven-day intervals, each dose containing six thousand million of the several types of pneumococcus.

More recently Cecil and Austin,¹¹⁷ at the Rockefeller Institute and at Camp Upton, have carried out elaborate studies on the preparation and dosage of the vaccine and have inoculated more than 12,000 soldiers. Types I, II and III pneumococcus were incubated 12-14 hours in 0.5 per cent glucose broth and then killed by heating to 53° C. for half an hour. The culture medium was removed by centrifugation and the cocci were suspended in salt solution. Viewed from the standpoint of protection alone, they found this vaccine equally efficacious in single or multiple injections, provided the total dosage in each case was the same. Fewer local and toxic reactions followed the use of repeated small inoculations. The optimum immunity response was obtained after three to five moderate doses at three- to seven-day intervals, or when seven small daily injections were given. The total dosage was six to nine billion of Types I and II, and four and one-half to six billion of Type III.

During ten weeks of observation of vaccinated cases no case of pneumonia developed among the men who had received two or more injections of vaccine, whereas in a control series of about 20,000 men there were 26 cases of pneumonia due to pneumococcus Types I, II and III.

The local sterile infiltrations that occasionally followed the injections disappeared spontaneously and were interpreted as an expression of cutaneous hypersensitiveness.

The results of this experience are striking and warrant an extensive application of the method.

For convenience of description the treatment of "pneumonics" may be considered under the headings: I. General; II. Symptomatic; III. Specific.

General Management.—In treating patients with pneumonia several facts must be borne clearly in mind.

Pneumonia is a self-limited disease and, depending upon the virulence of the infection and the resisting power of the host, may present a picture of the greatest severity or may be merely a mild abortive syndrome. The mortality varies in different epidemics, seasons and localities, regardless of treatment, and the same clinical picture may arise following infection with organisms other than the pneumococcus.

Failure to recognize these fundamental theses has led to unwarranted enthusiasm regarding the efficacy of various modes of therapy and, through reaction, to therapeutic nihilism. These facts granted, it is at once apparent that no therapeutic procedure can be established as of value until it has been widely tested in large series of cases occurring in different epidemics, and unless very definitely beneficial results are seen in these as contrasted with those obtained in untreated controls.

Proper measures of **isolation** should be taken.

The patient, placed in bed, should be thoroughly **bathed and kept**

clean. To carry out these and all other details of care the services of a competent well trained nurse are invaluable. A culture of the **blood and of the sputum** should be made promptly to determine the type of organism responsible for the infection. **Daily or more frequent examinations** of the patient are necessary to ascertain the extent and progress of the pulmonary lesion, the degree of intoxication, the condition of the circulatory system, the development of complications, etc. The posterior thoracic regions should be investigated even in the very ill, otherwise a pleural exudate may be overlooked. During these examinations **unnecessary exposure** of and **unneeded exertion** by the patient should be avoided. Cough is provoked less often if he is turned on to the diseased side. The sickroom should be large, quiet, bright and well ventilated, the windows open, except during examinations or treatments. The bed should be a single one and of a type to facilitate attention on the part of nurse and physician. The coverings should be sufficient to protect the patient but not so heavy as to incommode him or to interfere with respiration. The bedwrap should be a light woolen shirt or pajama, slit the entire length to afford easy access for examination. The patient should not be permitted to sit up even to wash or feed himself and all attendants should be instructed to spare him effort. If he must be removed from his home to a hospital the greatest care must be observed to minimize physical activity, active or passive, during transportation.

The best position in bed is that which gives the greatest comfort.

Visitors should not be permitted during the active stage of the disease.

The **temperature, pulse and respiration** should be charted every two hours, day and night. Rigid care of the **mouth, nose and lips** is necessary. The **teeth** should be cleansed at least twice daily, the mouth rinsed with a **mild antiseptic solution** (Dobell's solution, liquor alkalinus antisepticus, etc.), and if the lips are very dry or fissured the application of **liquid vaseline** flavored with peppermint is often comforting.

The **total urine** should be collected and examined daily and the character and quantity of the **sputum** noted. Gauze used to wipe the nose and lips should be burned. Bed linen, sputum containers, thermometers and all utensils of the sickroom should be cared for as in other infectious diseases.

Drugs should not be administered unless there are definite indications. A dose of **morphine, codeine** or **Dover's powder** to relieve pain and restlessness may be administered provided there is no marked impairment of renal function. **Cardiac depressants** and **measures that lower blood pressure** are to be avoided. **Laxatives** may be given at the onset of the disease, if necessary. The best diuretic is **water or milk**. **Alcohol** should be given only in those cases in which it promotes appetite and helps digestion and in those addicted to the use of it. Small amounts of **brandy or whiskey** may be given to elderly patients as a food or as a hypnotic.

Expectorants, diaphoretics and stimulants are not indicated as routine procedures.

OXYGEN.—The evidence concerning the value of **oxygen** as a therapeutic agent in pneumonia is contradictory^{118, 119} due (1) to failure to clearly recognize the indications for the utilization of it and (2) to

faulty method of administration. Numerous observations have shown the prognostic significance of anoxemia in pneumonia and have established the presence of it as the primary indication of the administration of oxygen. The appearance of cyanosis or an increase of its intensity is the chief clinical sign of unsaturation of the blood with oxygen, so that when marked blueness appears, the need for oxygen has been shown to exist. Experience has taught that the inhalation of the gas from a mask or from a funnel fails to relieve the need because a sufficient concentration of oxygen cannot be obtained in the air inspired. The administration of oxygen through a nasal tube may be quite satisfactory in the mild and moderate grades of arterial unsaturation, but oftentimes, even in these, the benefits derivable from this procedure are minimized or more than offset by the discomfort caused, and in patients who have marked arterial anoxemia it is ineffectual. To be truly helpful, oxygen in the concentration of 40 to 60 per cent is needed and this may be had either in a chamber or room such as that devised by Stadie,¹²⁰ or in a portable tent made according to the plan of Barach and Binger.^{121, 122, 123} The latter device or a rebreathing apparatus with the use of a special nose-piece is the most efficient of the portable mechanisms.

Although often evidences of improvement are manifest promptly after treatment is instituted—lessening or disappearance of cyanosis, a fall of temperature, slowing of the pulse, diminished respiratory distress, promotion of sleep and decreased delirium—prolonged treatment may be needed completely to overcome anoxemia. It is to be emphasized that this therapeutic measure is supportive and not curative, and that it is of the greatest value if utilized as soon as the evidences of insufficient oxygenation are manifest.

DIET.—The diet in pneumonia may be arranged according to the desire of the patient and with regard for his ability to digest it. The disease is of such duration that a few days of restricted intake will do no harm. When there is anorexia or when gastric disturbances are present, a liquid diet, with feedings at intervals of two hours, suffices. In some cases from the onset, in others after the active febrile stage is past, a soft diet may be allowed, and in all cases when defervescence is established liberal meals with intermediate feedings should be given. Studies reported by Austin indicate that patients who have pneumonia receive as a rule too little salt in their food. According to him, the addition of 10 to 25 grams of sodium chloride to the diet is distinctly beneficial.

It is well to prohibit foods that cause distention, and if milk does not agree it may be peptonized, diluted with lime water or Vichy, or it may be given in the form of buttermilk, kephir, koumiss, malted or as junket.

Children must often be fed by gavage. In the aged it is well to give small amounts of food at frequent intervals.

The fluid intake should be liberal and it is well to have the patient take at least a quart of water daily in addition to the liquids in the diet. If water causes nausea, ginger ale, lemonade, grape juice, coffee, tea, albumin, etc., may be given in its stead.

HYDROTHERAPY.—**Hydrotherapeutic measures** are invaluable in the treatment of pneumonia. They not only bring about a lowering of the temperature with concomitant diminution of discomfort, but through the use of them the nervous system is calmed, the circulation is aided,

the blood pressure is raised, respiration is stimulated and increased elimination is promoted.

Cold sponges are the most generally useful. Sponging with cool or tepid water or with dilute alcohol may be repeated at intervals of 3 to 4 hours, regardless of the elevation of temperature. The extremities and trunk should be sponged separately and during the process massaged briskly, rubbing towards the body. A properly given sponging requires 15-20 minutes, during which care should be taken not to expose the patient to **chilling** and to prevent any avoidable exertion.

Internal hydrotherapy—the taking of an abundance of water—should be ordered in every case to promote elimination.

ÆROTHERAPY.—It is often difficult to convince the patient and his family that fresh air is a valuable accessory in the treatment of pneumonia and that temperatures of 60° F. (15.6° C.) are not harmful to the patient. The day of the overheated room with sealed windows passes hard. It lingers here and there with the use of the pneumonia jacket, poultices and the application of pastes to the chest. Regardless of the outside temperature, the **windows should be open**, and whenever conditions allow the **bed** may be wheeled on to a **protected porch**.^{124, 125} Of course, the clothing and covers should be sufficient amply to protect the patient, and nurses or other attendants should wear extra wraps. Fresh air makes respiration easier, stimulates the circulation, quiets the nervous system, promotes appetite and, according to statistics, lowers the mortality of the disease.

Treatment of Symptoms.—**CHILL.**—The patient should be **warmly clad**, wrapped well with **blankets** and surrounded by **hot water bottles** or an **electric pad**. A **warm drink or whiskey** may be given.

FEVER.—Fever is a manifestation of infection and an evidence of the resistance of the host. Except when hyperpyrexia is marked or when the fever itself is a cause of discomfort, there is no object in seeking to reduce it. The use of **antipyretic drugs** is to be condemned, and **hydrotherapy**—external and internal—is the method of choice to give relief from this symptom.

THORACIC PAIN.—Thoracic pain often distresses the patient to such an extent as to prevent relaxation or sleep, and may cause exhaustion. It is often relieved by the application of **cold** (ice-cap—Leiter's coil) or of **heat** (hot water bag, electric pad) to the chest wall. The use of **counterirritants**, of **cupping** or of **leeches** is undesirable. **Fixation of the thorax** with a taut binder may be helpful, and though similar relief is afforded when adhesive straps are used, the latter are objectionable because they interfere with examinations and often irritate the skin.

When these measures do not avail a **sedative** may be administered. **Opium** and its derivatives, **Dover's powder**, grains 5-10 (0.325-0.65 gram), and **codeine**, grain $\frac{1}{4}$ - $\frac{1}{2}$ (0.016-0.03 gram), are of great value in pneumonia for they not only relieve pain but promote relaxation and sleep.

COUGH.—Cough is a symptom that requires medication only when it is harassing. To check repeated unproductive paroxysms **codeine sulfate**, grain $\frac{1}{8}$ - $\frac{1}{4}$ (0.008-0.016 gram); **heroin hydrochloride**, grain $\frac{1}{12}$ (0.005 gram), or **morphine**, grain $\frac{1}{8}$ (0.008 gram), hypodermatically or by mouth, may be given. Of these drugs heroin is the least desirable and it is to be used with great caution. **Expectorants** are

rarely helpful. In every case it is important to exclude a complicating pleural effusion as the provocative cause of the symptom.

PLEURAL AND PULMONARY COMPLICATIONS.—The treatment of pleural and pulmonary complications (abscess, gangrene and delayed resolution) has been considered in the section on Complications.

CIRCULATORY SYSTEM.—The readiness with which signs of circulatory asthenia can be detected has given rise to a false impression of the relative frequency with which the heart and the vasomotor centers are materially damaged in lobar pneumonia, and failure to appreciate that often the lethal outcome is secondary to a general infection with the pneumococcus.

Anatomical and experimental studies have shown that the myocardium is rarely diseased in lobar pneumonia. Experiments of Newberg and Minot indicate that the cardiac embarrassment encountered is often one of the manifestations of infection and intoxication. They showed that the heart of an animal with pneumonia contracted normally when perfused with the blood of a normal animal, but that it failed to do so when the blood of an animal ill with pneumonia was utilized, although, if, in the latter experiment, such blood was introduced slowly, the heart could still function adequately.

Generally speaking, when the circulatory mechanism fails in lobar pneumonia, the evidences of incompetence develop rapidly and local signs of myocardial weakness seldom antedate for an appreciable time complete failure. However, in some instances increasing tachycardia, deteriorating quality of cardiac sounds, the appearance of arrhythmias or of pulmonary edema may presage collapse for a time. Recognition of this group has stimulated the search for a method to forestall the progress of circulatory embarrassment.

Undoubtedly, the best of such prophylactic measures are those that protect the patient and lessen the intoxication, such as the avoidance of unnecessary effort, excitement or annoyance; careful regard for every detail that insures comfort and the needed relaxation and sleep; the lessening or abolition of pain, of cough, of distention, etc.

Concerning the value of cardiac stimulants so-called, and more particularly, of *digitalis* and of *strophanthus*, opinion is unsettled. Many competent clinicians consider it wise to withhold digitalis or similarly acting drugs so long as there are no evidences of circulatory weakness. Other equally experienced and capable physicians, mindful of the time required to bring about the full effect of such preparations, advocate the administration of them routinely to all patients, so that should the indications for the use of them arise, a prompt effect could be obtained. In the opinion of the author, the latter method is preferable provided the drug is given in amounts insufficient to produce toxic symptoms (nausea, vomiting, etc.).

In recent years a number of accurately standardized potent preparations of digitalis have been made available and so long as such an one is chosen it matters little which one it is. Tinctures are generally standardized now so that one c.c. contains one cat unit and dry preparations so that 0.1 gm. contains a like amount. A cat unit is the amount of digitalis per kilogram of cat required to kill the animal when it is injected slowly and continuously into the femoral vein.

If rapid digitalization of the patient is desired, the drug may be given in accordance with the so-called "body-weight" method of Eg-

gleston, by which method a full effect can be secured within 24 hours or less if 1 cat unit is given for each 10 pounds of the patient's weight. Thus, to digitalize an adult weighing 150 pounds would require 15 c.c. of the tincture or 1.5 gm. of the powdered leaf. Depending upon the urgency of the situation, from $\frac{1}{3}$ to $\frac{1}{2}$ of this total may be administered in the first dose, $\frac{1}{3}$ to $\frac{1}{4}$ of the total after 4 or 6 hours, and smaller proportions at intervals of 4 hours thereafter until the calculated amount has been given or the desired effect has been produced. When the drug is given thus, careful observation of the patient before, during and after the procedure is necessary if toxic effects are to be avoided. This intensive treatment is contraindicated if digitalis has been taken within several preceding days.

When restlessness, pain or cough seems to endanger the cardiac reserve the addition of **dionine** gr. $\frac{1}{4}$ - $\frac{1}{2}$ (0.0166-0.0333 gm.) to each dose of digitalis has proved of real value in the author's experience.

When gastro-intestinal symptoms are present or when the patient can not or will not take the drug by mouth, one of several preparations of digitalis may be given intravenously or subcutaneously. The intravenous injection of the drug is not without danger and it is to be avoided if the patient has received digitalis within the preceding 36 hours. The method is employed less frequently now than formerly. For subcutaneous injection **digitalein** gr. $\frac{1}{60}$ to $\frac{1}{30}$ (0.001-0.002 gm.), **digifolin** 15-30 minims (1 to 2 c.c.), **digalen** 10 to 15 minims (0.6-0.92 c.c.) or **digitan** 15 minims (1 c.c.) administered every 4 hours as long as needed are useful.

If there is no necessity rapidly to secure the full effect of the drug, oral administration of a fresh, standardized tincture may be given in doses of 10 to 30 minims (0.6-2 c.c.) three times daily so long as toxic symptoms do not develop and the need for it seems to exist, or 1.5 to 3 gr. (0.1-0.2 gm.) of a similarly standardized powdered leaf may be given. These two preparations are quite satisfactory and are much less expensive than most of the more refined preparations of digitalis from which substances that irritate the digestive tract have been removed.

The preparations of *strophanthus* fail generally when those of digitalis are without effect, but now and again when cardiac failure develops acutely, **amorphous strophanthin** gr. $\frac{1}{120}$ - $\frac{1}{60}$ (0.0005-0.001 gm.) or **crystalline strophanthin**, known as ouabain, gr. $\frac{1}{200}$ - $\frac{1}{120}$ (0.00032-0.00054 gm.) seems to be of benefit. These drugs should not be given if digitalis has been taken recently, nor should the injection of them be repeated.

When acute dilatation of the right side of the heart develops, a liberal **venesection** with the removal of 250 to 500 c.c. of blood may tide over the emergency. When there is evidence of stasis in the lesser circulation with pulmonary edema, **atropine** is a valuable accessory. It may be given subcutaneously or orally in doses of gr. $\frac{1}{100}$ - $\frac{1}{50}$ (0.00065-0.0013 gm.) and repeated at intervals of 3 or 4 hours until the physiological effect is noted.

Strychnine as a stimulant of the circulation has not proved of value in the author's experience. A large and polemical literature on the worth of this drug in pneumonia indicates considerable confusion as to its efficacy.

Caffeine sodium benzoate, gr. 3 (0.195 gm.), or **epinephrine** minims 15 to 30 (0.92 to 1.9 c.c.) may be given hypodermically when a rapid, transitory stimulation is desired.

Camphor in oil, coramine, metrazol and nitroglycerin have not proved of value in the writer's experience, nor has alcohol seemed to influence a failing circulation.

The **aromatic spirit of ammonia** may be useful at times when cardiac palpitation accompanies abdominal distention or nausea.

When the symptoms of vasomotor collapse (*q.v.*) supervene, it is helpful to elevate the foot of the bed, to give centripetal massage to the lower extremities and then to bandage them snugly from the feet to the hips, to place a binder about the abdomen and to inject hypodermically **epinephrine** (0.5 c.c. every 30 to 60 minutes) or **pituitrin** 0.5-1 c.c.

GASTRO-INTESTINAL SYSTEM.—*Anorexia* rarely requires treatment.

The *bowels* should be regulated throughout the disease. A **purgative** may be administered at the onset of the disease (sodium phosphate, Eidlitz powder, calomel, etc.), and during the course of the disease a **soapsuds enema** given daily or every other day not only will relieve constipation but often will lessen discomfort due to tympanites. When *distention is marked*, **restricted diet**, **enemata**, plain or medicated, **hot stupes**, **turpentine stupes** or the use of a **soft rectal tube** passed high into the bowel and left in position for an hour or more, will often suffice. If these measures fail, a **hypodermic injection of pituitrin** 1 c.c. is an excellent remedy.

For *acute dilatation* of the stomach **repeated lavage** may be necessary. *Incessant vomiting* may be relieved by **limited diet**, **ice compresses** or a **mustard plaster** applied to the epigastrium and by the use of **gastric sedatives**.

Colitis is relieved by **correction of the diet** and the use of **irrigations of the bowel** with solutions of salt, alum or boric acid.

Persistent hiccough may require the administration of **codeine**, **pan-topon** or **morphine**.

Peritonitis and other intra-abdominal complications of inflammatory nature demand **prompt surgical intervention**.

NERVOUS SYSTEM.—*Headache* is usually relieved by the local use of the **ice-cap** or of **cold compresses**. Less often drugs are indicated and then **acetyl salicylic acid** gr. 5 (0.324 gm.), alone or with **codeine sulfate**, gr. $\frac{1}{4}$ - $\frac{1}{2}$ (0.016-0.032 gm.), or with **camphor monobromate**, gr. 1 (0.065 gm.), is usually effectual.

Insomnia may be relieved by the use of **hydrotherapy**, by the **relief of pain**, or it may require the use of **hypnotics**. **Codeine** or **morphine** may be used: or if there is no cardiac weakness the usual dose of **sulfonal**, **veronal**, **trional** or **paraldehyde** may be given. **Chloral** is a depressant and must be used with great caution.

Delirium is quieted by **sponging** or by the use of the **sedatives** already mentioned, though **morphine** is rarely of service. **Lumbar puncture** with withdrawal of small amounts of fluid has been recommended when other measures fail,¹²⁶ but it is to be avoided if possible. In alcoholics it is lessened and may be prevented by the use of **whiskey**, **brandy**, etc., and in these cases **depressant drugs** are contraindicated. When an *exhaustion psychosis* develops, a **full diet** and **general up-building measures** are to be employed.

In every case with marked cerebral symptoms the presence of otic and of meningeal complications and the development of sepsis must be excluded. *Meningitis* is a very fatal complication but the use of **specific antipneumococcus serum alone or with optochine intraspinally** is indicated.

GENITO-URINARY COMPLICATIONS.—Genito-urinary complications are very infrequent. When nephritis develops it requires the same measures as do other forms of acute nephritis—**protection from chilling, a purine-free, protein-poor diet** with restriction of **salt**, regulated intake of **water** and stimulation of the excretory activities of the **skin and bowels**. In the very acute cases intravenous injections of solutions of **glucose** may be of value (100–500 c.c. of a 2 per cent solution).

SKIN.—The *skin* requires the careful attention needed in all patients confined to bed. *Herpes* may be dried by the use of dusting powders such as **zinc oxide, stearate of zinc, etc.**, sedative washes such as **camphor water, compound tincture of benzoin, spirits of niter**, or ointments, such as **oxide of zinc** with or without **cocaine**.

THE CRISIS.—At the time of crisis, during it and after its occurrence, **protection and support** are needed. The patient must not exert himself; he should be kept recumbent, not allowed to strain at stool or to feed himself. If indicated, **stimulants** must be promptly administered in rapidly diffusible form. Hypodermic injections of **caffeine, sodium benzoate and atropine** are the ones of choice.

Warm coverings and hot water bottles, the electric pad or heat applied in other ways are often of use.

CONVALESCENCE.—Though the period of convalescence after a mild attack need not be long, several weeks of **rest** with abundance of **fresh air, a full diet** and slowly increasing periods of **exercise** should be taken. When the disease has been severe with marked intoxication or a prolonged course it is wise to refrain from working for a longer period, and an abundance of **rest, fresh air and good food** with **general massage** before active exercise is permitted, are the best aids to complete recovery of normal strength. If cardiac or pulmonary complications have caused organic or functional disability, a proper régime should be ordered with **graduated exercise**, and **cardiac stimulants** if there is circulatory asthenia, and **respiratory gymnastics** and **change of climate** if there is pulmonary impairment.

Tonics, hematronics, etc., are rarely needed, as anemia is uncommon after pneumonia.

TOXEMIA.—The manifestations of toxemia must be overcome chiefly by the use of general measures. They are often distinctly lessened by **hydrotherapy, aërotherapy, eliminants and stimulants**. Continuous or intermittent **enteroclysis of salt solution** is helpful. **Hypodermoclysis** may be given, or if a more prompt effect is needed, **intravenous injections of salt solution** or of **solutions of glucose** may be employed.

In some cases large doses of **alkali** (bicarbonate of soda 15 gr. [1 gm.] or more several times daily) seem effectual, and these may be supplemented by the intravenous injection of a sterile 2 per cent solution of **glucose** if acidosis is marked.

The usefulness of **alcohol** in cases with marked toxemia is moot, but there seems little doubt that its value is slight, except in those habituated to the use of it, in the aged or in those who cannot take sufficient nourishment.

When there are evidences of circulatory failure the procedures already outlined should be employed.

DELAYED RESOLUTION.—**Local and general measures** may aid in restoring the lung to function. **Counterirritants** and injections of **fibrolysin** are without value. **Pulmonary exercises** (breathing against resistance, *i.e.*, use of water bottles, etc.) are helpful in some cases. The use of the **x-ray** has been said to exert a decidedly beneficial influence.¹²⁷ **Thoracotomy**¹²⁸ has been recommended in some cases. The upbuilding of the patient by the use of **overfeeding, rest and fresh air**, together with tonic preparations, such as **sodium cacodylate**, gr $\frac{1}{4}$ (0.048 gm.), hypodermatically, **iron**, etc., hastens recovery.

Specific Therapy.—**SERUM THERAPY.**—Since Pasteur's observation that animals could be immunized against pathogenic organisms, and more particularly since von Behring demonstrated that it was possible passively to immunize animals by the injection of the serum of those treated with diphtheria toxin, numerous attempts have been made to produce an antipneumococcus serum with potent prophylactic and curative properties. The great obstacle to success was the fact that no soluble toxin could be isolated from the pneumococcus, and until it was shown experimentally that the injection of sublethal doses of living pneumococci protected against subsequent injections of lethal doses, the outlook for the production of an efficacious antipneumococcus serum was dark. Fränkel¹²⁹ demonstrated that an antiserum was responsible for the protection that resulted from such treatments and that though it was not antitoxic it could be used to immunize animals passively. The Klemperers,¹³⁰ in 1891, were the first to test the efficacy of such an antibacterial serum in the treatment of pneumonia, and their results stimulated further investigations, among the more important of which were those of Römer,¹³¹ Pane,¹³² Neufeld and Händel,¹³³ and the contributions from the hospital of the Rockefeller Institute.

In 1904 Anders¹³⁴ concluded from a review of the literature that though the data were insufficient to justify optimism, they were sufficiently suggestive to warrant further investigations.

To Neufeld and Händel¹³³ belongs the credit for the first preparation of a useful serum. They suggested the need of using large intravenous injections of virulent pneumococci to immunize animals, demonstrated the specific antigenic properties of the several types of the organism and stressed the fact that a proper serum cannot be had for treatment until it is ascertained what particular strain is responsible for the infection in a given case. They also devised a method of standardizing the serum and recommended the intravenous administration of at least 75 c.c.

Dochez and Gillespie¹³⁵ isolated numerous strains of pneumococci, and on the basis of specific biologic relationships established the subdivision of the pneumococcus into four definite Types, I, II, III and IV. The immunization of horses by intravenous injections of a given strain led to the production of an antiserum of fair potency against Types I and II and with maximum power of protection against other strains of the homologous type. As yet no satisfactory serum has been prepared for Types III and IV.

Inasmuch as a given antiserum is most active in protecting against infection with a strain of pneumococcus homologous with that by which it was produced, no constant therapeutic results are to be expected un-

less the type of pneumococcus responsible for the infection is determined; for only then can a proper antiserum be administered.

Practically, the procedure is as follows: After the clinical diagnosis has been made and the specific strain of the causal agent has been identified, the patient is given a subcutaneous injection of 0.5–1 c.c. of horse serum to test for the presence of hypersensitiveness. Even when this test is negative, it is safer in all cases to give 1–5 c.c. of horse serum subcutaneously as a desensitizing dose before administering a large volume of the antiserum. The danger of an immediate reaction to the serum overcome, 50–100 c.c. of the warmed antipneumococcus serum diluted with an equal amount of sterile 0.85 per cent salt solution are injected intravenously at the rate of 2–4 c.c. per minute. The injection is repeated every 6 or 8 hours until conditions indicate that there is no need for further treatment. The only harmful effects that may result are those that follow so often the administration of foreign sera (serum sickness, *q.v.*).

A large number of patients with pneumonia have been treated by this method, and the published statistics indicate that when the injections are given early in the disease due to infection with Type I pneumococcus, the results obtained are encouraging. In 65 cases treated at the hospital of the Rockefeller Institute the mortality was reduced from 25 to 7.5 per cent.¹³⁶ In a series of 11 cases at the Johns Hopkins Hospital¹³⁷ the effect of similar treatment was less striking.

In 1924 Wadsworth¹³⁸ reported a series of 445 cases treated with Type I serum by a large number of physicians without effect upon the mortality of the disease, and in 1925, Locke¹³⁹ published a study of 145 cases of Type I pneumonia treated with serum with no apparent lowering of the death rate.

Acceptable explanations for the failure of the serum in these and in comparable studies to influence favorably the outcome of pneumonia due to Type I pneumococcus are (1) the patients were not treated sufficiently early, (2) the serum may not have been potent enough, (3) the dose administered may have been insufficient, (4) the administrations of the serum may have been too few.

Following an injection of serum, the temperature may remain elevated, to fall by crisis at the customary time; or defervescence may occur gradually within a few days. Generally, the course of the disease is shortened, the pulse is slowed, the cyanosis lessened and the evidences of intoxication are fewer than in untreated cases. Often, within an hour or less after the administration of the serum, there is a chill and a rise of temperature, followed often by a sweat and then an abrupt decline of the fever. A subsequent rise usually occurs and these phenomena may be repeated after each injection.

The large amount of serum needed and the reactions that follow not infrequently the injection of horse serum have been deterrents to the general utilization of this therapeutic agent.

HUNTOON'S PNEUMOCOCCUS ANTIBODY SOLUTION.—In 1921 Huntoon¹⁴⁰ sought to obtain pneumococcus antibodies freed of serum. He suspended pneumococci of Types I, II and III in a large amount of a trivalent serum obtained from horses that had been inoculated with pneumococci of these types. The bacteria, united with the antibodies, were removed by centrifugalization and washed free of serum with saline solution, emulsified in saline solution containing 0.25 per cent of bicar-

bonate of soda and heated from 30 to 60 minutes at 55° C. The emulsion was then centrifugalized, the supernatant fluid was chilled and filtered through a candle. The filtrate obtained by this method is a clear, colorless fluid and contains only a minimum trace of serum and a high content of antibodies against pneumococcus Type I and a very little of the antibodies for Types II and III.

Cecil¹⁴¹ demonstrated that this polyvalent antibody solution had real value when used in the treatment of pneumonia produced experimentally in monkeys by the injection of pneumococcus Type I, less effect when injected into animals infected with pneumococcus Type II and no value when injected into animals infected with pneumococcus Type III. Cecil and Larsen¹⁴² treated patients with pneumonia at Bellevue Hospital and noted an appreciable lessening of the mortality of pneumonia due to pneumococcus Type I, especially when the treatment was given within the first 4 days of the disease.

Following the intravenous injection of this solution, a sharp febrile reaction with a chill, cyanosis and dyspnea occurred in many cases within 20 to 40 minutes. The high fever lasted from 30 to 60 minutes and then there was a sharp fall of temperature. These reactions followed each injection but were less severe with each successive treatment. That such responses are to a degree nonspecific and that they are due to the foreign protein was indicated by the effect of the serum in pneumonia due to infection with pneumococcus Type IV, in which also there was a decrease of the death rate.

The value of the treatment was lessened by occasional fatalities that followed sharp reactions. When the effort was made to offset these untoward effects by injecting the serum subcutaneously, no effect on the outcome of the disease was noted.

The purified solution of pneumococcus antibodies of Huntoon now obtainable in the market can usually be administered without causing a thermal reaction if no more than 50 c.c. are injected, but as larger doses (100 to 150 c.c.) are required for a therapeutic effect, systemic reactions cannot be avoided.

FELTON'S CONCENTRATED ANTIPNEUMOCOCCUS SERUM.—In 1924 Felton^{143, 144} observed that the protective substances in antipneumococcus sera were always contained in the globulin fraction of the serum and that the greatest concentration of them could be obtained in the precipitate that followed dilution of the serum with 15 parts of cool, distilled water. The flocculent precipitate that settled over night in the ice-box was washed again with the same volume of cool, distilled water, and after it had settled once more, the sediment was rewashed, collected by means of a Sharpless centrifuge, dissolved in 0.5 molecular salt solution or tartaric acid, and if the solution was not clear, it was passed through a Berkefeld filter. With this method from 2 to 3 times the concentration of antibodies present in the serum was obtained. When this purified, more potent product is injected intravenously, more than 10 per cent of the patients have a thermal reaction, an incidence about equal to that which follows the injection of unconcentrated serum.

Cecil demonstrated a definitely curative effect of Felton's concentrated serum in the treatment of pneumonia experimentally produced in monkeys with pneumococcus Types I and II, and noted that similarly favorable results with a lowering of the death rate followed the intravenous injection of this preparation in these types of pneumonia in

man, provided that the treatment was started within the first three or four days of the disease. The serum was distinctly less efficacious in those infected with pneumococcus Type II. In the patients and in the monkeys that were treated, the temperature fell promptly, pneumococci disappeared from the blood and the onset of crisis was hastened.

In summary, it is apparent that:

(A) The injection intravenously of a specific antiserum may influence the course and lower the death rate of lobar pneumonia that is due to infection with the pneumococcus Type I provided that (1) a potent serum is utilized, (2) the treatment is instituted early in the course of the infection, and (3) sufficient serum is administered.

(B) There are derivatives of specific sera that contain immune bodies in concentrated form with a minimum of the proteins of serum (Huntton and Felton), the injection of which may influence favorably the course and the outcome of pneumonia due to pneumococcus Type I, and when such concentrated purified preparations are utilized, the occurrence of undesirable and of serious reactions to foreign protein is less frequent.

(C) Although similar sera may be helpful occasionally in the treatment of pneumonia due to pneumococcus Type II, they are distinctly less so than is the specific serum in the treatment of pneumonia due to pneumococcus Type I.

(D) At present no comparably potent sera are available for the treatment of infections with pneumococcus Types III and IV.

(E) Fairly to evaluate the worth of antipneumococcus serum in the treatment of lobar pneumonia, the following injunctions should be observed: (1) Inasmuch as the introduction of a foreign protein into the circulation of an acutely ill patient is not without danger and because the constitutional and thermal reactions induced by such injections may disturb an already unstable balance, the administration of a serum should be preceded by the determination of sensitiveness to it, and if it is present, desensitization should be brought about. (2) As beneficial effects are to be expected only when the pneumonia is due to pneumococcus Type I or II, serum should be withheld until the type of the microorganism responsible for the disease has been determined.

Delayed resolution and empyema are as frequent in patients with serum as in those untreated, but serum therapy apparently minimizes the danger of sepsis, and even when it exists the microorganisms may disappear from the circulation after the serum is administered. Immune bodies are present in the blood immediately after the first injection and they can be demonstrated throughout the course of the infection if repeated treatments are given.

The treatment with specific sera is still in an experimental stage and the practical extension of it must await the preparation of improved sera and be safeguarded by judicious estimates of the benefits that seem to result from the use of them.

VACCINE THERAPY.—Vaccines have been used extensively in the treatment of lobar pneumonia. The object of this procedure is to stimulate the production of protective substances, and though there is evidence that this occurs in experimental animals, it is doubtful if a similar effect will result when a relatively small number of organisms are introduced into a host that is already infected. Interesting statistics have been published by Stoner,¹⁴⁵ Leary,¹⁴⁶ Craig,¹⁴⁷ Eyre¹⁴⁸ and others, but objective evidence of benefit following treatment with vaccines is not

available, and until it is forthcoming it is difficult properly to estimate the value of the method. At the present time the usefulness of the procedure is not established.

Rosenow and Hektoen¹⁴⁹ noted beneficial results following the injection of **partially autolyzed pneumococci**. Treatment with vaccines of **sensitized pneumococci** has also been recommended.

CHEMOTHERAPY.—The number of drugs heralded from time to time as the remedial agent of choice in the treatment of lobar pneumonia speaks for the absence of specificity on the part of those utilized. **Guaiacol carbonate, camphor, creosote, quinine, the iodides, antimony, the salicylates, digitalis, iron and numerous other preparations** each has its champions. Each may have some value in the relief of symptoms; none is a specific curative agent.

Boehmeke's¹⁵⁰ observations on the prophylactic value of **camphor** in experimental pneumococcus infections have not been confirmed clinically.

Morgenroth^{151, 152} and his assistants noted that quinine and some of its synthetic derivatives protected mice against experimental infection with trypanosomes and discovered that a particular derivative of quinine

ethylhydrocupreine—possessed especially marked bactericidal action on the pneumococcus. Morgenroth showed that this drug had not only great prophylactic value but also marked curative properties in pneumococcus infections of mice, and obtained optimum results when it was administered in oil. Fränkel,¹⁵³ Moore,¹⁵⁴ Clough, Lapinsky¹⁵⁵ and others have confirmed these observations and ethylhydrocupreine or **optochine** has been used in the treatment of pneumococcus infections in men.

Moore and Chesney¹⁵⁶ recommended, in a man of average weight, an initial dose of grains 7 (0.46 gram) and grains 2½ (0.15 gram) every two and a half hours, until grains 23½ (1.5 grams) per twenty-four hours have been administered. From grain 0.37 to 0.4 (0.024 to 0.026 gram) of optochine per kilogram of body weight is needed to render the blood bactericidal, and the dosage should be calculated on the basis of the body weight. The drug is given until the symptoms of the disease subside unless toxic manifestations due to the preparation itself develop. These latter are apparently dependent upon the concentration of optochine in the blood and are less likely to follow the use of repeated small doses. The action of optochine is cumulative.

The ocular manifestations resemble those noted in amblyopia due to quinine, and they may appear after a small total dose of the drug. Mydriasis and dimness or loss of vision contraindicate further administration. In marked cases there is pallor of the retina and narrowing of the retinal vessels. Blindness may develop and persist for a week or more, and though central vision is restored, contraction of the visual fields may be permanent. But one case of permanent blindness has been reported.

The development of deafness is not a contraindication to further treatment.

The available statistics "show a marked lowering of the mortality rate in a fairly large series of cases of lobar pneumonia. The results in the treatment of pneumococcus meningitis have been less favorable, but in *ulcus corneae serpens* local applications of 1 to 2 per cent aqueous solutions have been strikingly helpful."¹⁵⁸

Extensive experimental studies to determine the effect of other derivatives of **cinchona** have been made by Solis-Cohen^{157, 158} and his as-

sistants. Though they demonstrated that quinine and its congeners possess some bactericidal action on the pneumococcus, it was less than that of optochine. They were unable to establish an experimental basis for any beneficial action of these preparations.

PROGNOSIS

Pneumonia is always a serious disease and the prognosis must be a guarded one, for the apparently mild case may suddenly change for the worse and a manifestly severe case may as abruptly improve.¹⁵⁹

Wells,¹⁶⁰ in an analysis of 233,730 collected cases, found a mortality rate of 18.1 per cent, and in a later collection of 465,400 cases calculated a death rate of 20.4 per cent. This is the average in most large series of cases. The death rate varies between 20 and 60 per cent.

Accurate prognosis is determined only after consideration of many factors, general and individual.

Influencing Factors.—**DOMINANCE OF TYPE OF PNEUMOCOCCI.**—The severity and mortality of pneumonia vary greatly in different epidemics regardless of location, physical conditions and therapeutic procedure. These facts are frequently overlooked, and more than one season of mild disease with low mortality rate has led enthusiastic advocates of a mode of treatment to exaggerated claims for a *therapia magna*. It is possible that the variations in the mortality rate from year to year may be dependent upon the seasonal dominance of different types of pneumococci.

AGE.—The age of the patient is another determinant of the outcome of the disease. In general, the death rate is especially high in infancy and early childhood; there is a diminished mortality rate between six years and the age of puberty, and an increasing death rate above the age of puberty. The maxima occur at the extremes of life, and in the older patients the large number of fatal results are due to complications and to the existence of arteriosclerosis or to other chronic diseases, manifest or latent.

SEX.—The death rate is higher in women than in men, as shown by Musser's figures of 26.9 per cent for women and 19.3 per cent for men.

PREVIOUS ATTACKS.—The mortality is lower in those who have had one or more previous attacks of pneumonia.

ALTITUDE.—The influence of altitude, long considered of importance, is recognized to be without influence on the course of the disease.

RACE.—The effect of race upon mortality is well shown by the statistics of the Johns Hopkins Hospital, by the studies of W. Kolle of pneumonia in the South African negroes, by a consideration of the death rate among the negro mine workers of the Rand and among the laborers in the Panama Canal Zone. In the last the mortality was highest among those most recently arrived in the country. The greater death rate is probably due to the unhygienic living conditions of the negro, the frequent presence of cardiovascular disease, of alcoholism and of syphilis as well as to a racial susceptibility to the disease. Jews and Italians have a smaller mortality, and according to the United States census reports, the mortality is higher in the foreign than in the native whites.

COMPLICATIONS.—The development of complications has a marked influence on the outcome of an attack of pneumonia, and the earlier they develop in the course of the disease, the more serious the outlook.

Meningitis is almost uniformly fatal. Serous and serofibrinous pleurisy do not materially influence prognosis, but purulent pleurisy (empyema) has a higher death rate (35-40 per cent). Acute endocarditis leads more often to a lethal result (60-70 per cent) than does chronic endocarditis, and pericarditis, though less serious than the former, is a grave development (50-60 per cent mortality). The occurrence of marked jaundice is a cause for concern.

ASSOCIATION WITH OTHER DISEASES.—The influence of existing diseases on prognosis has been considered. It is most evident in individuals with valvular heart disease, chronic nephritis, diabetes mellitus, cirrhosis of the liver, arteriosclerosis, alcoholism and malignant disease.

CLINICAL MANIFESTATIONS.—The clinical manifestations give valuable prognostic data. An insidious onset; marked hyperpyrexia (except in the very young): a very slight febrile reaction; a pulse rate of more than 125 beats per minute in adults; an enfeebled pulmonic second sound, gallop rhythm, cardiac arrhythmia or signs of dilatation of the heart; a marked or abrupt fall of blood pressure, especially if associated with an increasing tachycardia; periodic respiration or a respiratory rate in adults of more than 50 per minute; extreme cyanosis; marked toxic manifestations; persistent abdominal distention; a poor leukocytic reaction, and the presence of pneumococcal sepsis are of unfavorable significance. In many cases, though the general condition of the patient and the results of physical examination indicate a favorable prognosis, the results of blood cultures forecast conclusively an unfavorable outcome. The demonstration of more than a few colonies per cubic centimeter of blood, or the presence of Type I or Type II pneumococcus in the circulation, is always of grave import as, too, is the demonstration of Friedländer's bacillus or the *Streptococcus mucosus*.

RELATION OF TYPE OF PNEUMOCOCCUS TO MORTALITY.—The outcome of a given case of lobar pneumonia is influenced by the type of organism to which it is due, and though the severity of individual cases due to the different strains of pneumococcus varies, knowledge of the type of invading organism is of real prognostic value.

The statistics of the Hospital of The Rockefeller Institute show that the mortality of Type I infection is 25 per cent; of Type II infection, about 32 per cent; of Type IV infection, about 16 per cent, and of infection due to Type III, 45 per cent. Types I and II, the etiological agents in over 60 per cent of the cases included in this series, were responsible for about 62 per cent of all deaths in the cases observed.

The results of a survey reported by Cole in 1929 indicated a mortality of 10.5 per cent among all patients observed that were infected with Type I; of 27 per cent of those infected with Type II; of 41 per cent infected with Type III, and of 14 per cent among those with pneumonia due to Type IV.

Although the pneumonia due to Types II and III is the most severe and the most fatal, Types I and II cause more deaths because the incidence of the disease due to them is greater.

LOCATION AND EXTENT OF CONSOLIDATION.—These factors have an influence on the outcome of the disease. Involvement of an entire lung is more fatal than disease of a single lobe; consolidation of an upper lobe has a higher death rate than consolidation of a lower lobe; pneumonia

of the right side has an apparently greater mortality than pneumonia of the left side. These facts are admirably illustrated by the tabulated statistics of Sears and Larrabee:

One lobe	31.0 per cent.
Two lobes	38.2 per cent.
Three lobes	59.0 per cent.
Four lobes	62.5 per cent.
Five lobes	100.0 per cent.
Double pneumonia	42.5 per cent.

as well as by Preble's tables:

Right upper lobe	20.0 per cent.
Right middle lobe	14.7 per cent.
Right lower lobe	17.2 per cent.
Right lung	42.0 per cent.
Left upper	18.9 per cent.
Left lower	14.4 per cent.
Left lung	27.1 per cent.
Bilobar	36.2 per cent.
Bilateral	35.5 per cent.

Modes of Death.—Over 50 per cent of the deaths occur between the fifth and the twelfth day of the disease. Sudden death may occur during the course of the disease or after convalescence has been established, due to sudden dilatation of the heart, to cardiac or pulmonary thrombosis. An abrupt termination may happen independently of the apparent severity of a given case and without relation to the extent of the pulmonary involvement.

Often the fatal result is foretold by a period of cardiac decompensation or by signs of increasing toxemia. More commonly, certain untoward symptoms herald the coming end. As early as the first day—most often at the height of the disease and uncommonly during convalescence—a patient who has been doing well may develop stupor, delirium, increasing polypnea, dyspnea and cyanosis, an increasingly rapid and weakened pulse or cardiac arrhythmia. Signs of collapse appear with clammy skin, exhaustion, evidences of pulmonary edema, profound intoxication and a rise or fall of temperature just before death occurs. Death of this type is probably due to the development of pneumococcus sepsis or to an advancing infection of the lungs.⁵⁸

The clinical syndrome known as "vasomotor collapse," characterized by evidences of marked vasodilatation, has been shown experimentally to be independent of exhaustion of the vasomotor center. The explanation for this complex is not established but it may be due to an undiscovered general infection.

Only when the making of repeated blood cultures in lobar pneumonia is established as a routine measure will there come an accurate and general realization of the importance of sepsis as a cause of death in this disease.

Duration.—The duration of the disease varies considerably. The average duration of uncomplicated cases is from six to twelve days and it is rarely longer than three weeks. Abortive attacks are not uncommon, and true one-day pneumonia is occasionally seen. When com-

plications occur the course may be unusually protracted, especially in cases of delayed resolution, organizing pneumonia, pneumonia migrans and empyema.

In cases of sepsis death may occur on the first day before the signs of pulmonary consolidation are manifest, but as a rule it does not occur before the fourth or fifth day.

Termination.—The febrile stage ends by crisis in over 50 per cent of the cases, but though with the critical defervescence the subjective symptoms usually subside, signs of resolution do not appear immediately, and an appreciable period elapses before the leukocytic curve and the excretion of urinary chlorides return to normal. In about a third of the cases the fever terminates by lysis or by retarded crisis.

Following crisis there is often a short period of hypothermia that is of no significance unless it is prolonged and accompanied by tachycardia, when it may be indicative of exhaustion.

In typical crises the temperature reaches normal within 6 to 20 hours; but atypical crises occur, and 24 to 40 hours elapse before defervescence is established.

Pseudocrisis is distinguished from true crisis by a recrudescence of fever after it has reached normal and remained so for several hours. It is usually followed by crisis within a day or two.

Termination by lysis is more common in some epidemics than in others and occurs more often in protracted cases, when complications have developed, in mixed infections and in those with other acute or chronic diseases.

Relapse.—True relapses are rare in lobar pneumonia and it is in the abortive short-term cases that they are most likely to develop. The term should be used to describe those cases in which, after defervescence has been established and signs of resolution have appeared, evidence of a reconsolidation of the affected lung tissue develops with a recrudescence of fever. Several relapses, each usually of short duration, may occur.

The term "recurrent pneumonia" is used to designate a second attack of the disease after an appreciable period of freedom from symptoms.

PATHOLOGY

Anatomically lobar pneumonia is characterized by inflammatory changes which take place in the lung, due to the action of pneumococci. These changes develop in a continuous sequence and it must not be inferred that, because traditionally these changes are divided into several stages, they are distinct or inherently different processes. For convenience of description the pathological processes are divided into a stage of engorgement, of red hepatization, of gray hepatization and of resolution, but it is rare to find solely the lesions characteristic of a given stage.

Stage of Engorgement.—This is the earliest manifestation of pneumonitis and is rarely seen at autopsy except when a pneumonia is spreading or when the patient dies from some other cause than the pneumonia. The change is vasodilatation with engorgement of the lung parenchyma and the exudation of serum with a few red corpuscles and leukocytes into the alveoli. The lung at this stage is deep red in color, its volume greater than normal; but though it is of increased firmness it is air-containing. The cut surface exudes a bloody serous material, and

microscopical examination shows engorged, distended capillaries, arteries and veins, swollen alveolar epithelium and coagulated serum with a few blood cells, red and white. Fibrin is present but is inconspicuous. This stage of inflammation lasts but a few hours before red hepatization develops.

Stage of Red Hepatization.—In this, the second stage of hepatization, the involved lung is reddish-brown in color, voluminous, heavy, non-air-containing and sinks when immersed in water. The surface has lost its normal sheen and is lusterless, often covered with a layer of fibrinous exudate. When sectioned it is found to be friable, firm and airless, and the cut surface is dry and very granular in appearance. When scraped with a knife very little moisture is expressed, but fibrinous plugs from alveoli and bronchi often rise above the surface. These vary greatly in diameter, depending upon the age of the patient and upon the presence or absence of antecedent emphysema.

On microscopical examination the alveoli are seen to be distended with an inflammatory exudate very rich in fibrin, pneumococci, red corpuscles, leukocytes, desquamated alveolar epithelial cells and often numerous wandering cells or lymphocytes. The fibrin is present as a network, in the meshes of which the cellular elements are trapped. The very distinctive feature of this stage, in addition to the amount of fibrin, is the freshness of the exudate and the preservation of the cells. The red cells are more numerous than in the later stages, are intact, clearly outlined and show no evidence of hemolysis. The leukocytes are predominantly of the polymorphonuclear neutrophilic variety and often show engulfed pneumococci.

The alveolar walls, the peribronchial and perivascular tissues are edematous and infiltrated with leukocytes. The smaller bronchi may be plugged with fibrinous exudate. The blood vessels may be patent, often they are compressed, and they may be occluded by thrombi. The lymphatics are distended with serum, fibrin and leukocytes.

Stage of Gray Hepatization.—In the stage of gray hepatization the color has changed to reddish-gray or gray. The lung is still enlarged, firm and non-air-containing. The surface is covered by a thick plastic exudate that can often be peeled off in layers from the adherent lung underlying it. The cut surface is mottled, the variations in color doubtless due to the laking of the red cells and the metamorphosis of the discharged hemoglobin. The tissue is more moist and a turbid fluid can be expressed from it. It is also less friable and is less granular in appearance.

On microscopical examination the alveoli are found closely packed with an exudate that consists mainly of polymorphonuclear leukocytes, pneumococci, both extracellular and intracellular, with relatively less fibrin and fewer red corpuscles. Especially distinctive of this stage, in contrast to that of red hepatization, are the cellular richness and the degeneration of the cellular elements of the exudate. Very few intact red corpuscles are found, but the shadows of the laked cells are seen. The leukocytes likewise show marked disintegration, and some contain fat droplets and blood pigment as well as pneumococci. In this, as in the preceding stage, fibrin threads may be seen passing through the alveolar walls through the so-called "pores of Cohn," and an occasional megakaryocyte may be found within the alveolar capillaries. The fibrin is

often granular by this time and the desquamated alveolar epithelial cells are numerous.

The capillaries of the alveolar walls are often extensively plugged with fibrin (Kline and Winternitz)—a factor that may be of importance in the process of resolution.

Stage of Resolution or Purulent Softening.—In this stage the enlarged lung is soft, friable, curiously translucent and jelly-like. This condition is rarely seen at autopsy except in cases of pneumonia migrans and when death has resulted from an intercurrent infection. The striking finding on microscopical examination is the very advanced disintegration of the cells of the exudate, which are often quite fatty. Occasionally marked phagocytosis is seen, and there may be evidences of epithelial repair. The exudate is liquefied by the action of proteolytic enzymes furnished by the leukocytes, and the bulk of the inflammatory material is removed by absorption.

The stage of repair, of restoration of the alveolar epithelium after the removal of the exudate, is even more rarely seen. It is remarkable how little involvement of the lung tissue itself occurs in pneumonia. The entire process seems to occur in the alveolar spaces and involves only the superficial epithelium of the air spaces, so that the complete restoration of the lung is readily brought about after the inflammation subsides.

Organization or carnification of the exudate may take place in exceptional cases. The exudate, instead of undergoing resolution and absorption, is invaded by blood vessels and fibroblasts, with resulting fibrosis of the lung. The cells of the alveolar walls proliferate, new connective tissue grows into the exudate, capillaries form and a new fibrous tissue replaces the inflammatory tissue. The lung is now firm and elastic, reddish-brown in color and often covered with dense fibrous adhesions. When the exudate is thus replaced, the lung is essentially functionless and the condition is variously described as an organizing pneumonia, chronic interstitial pneumonia, pulmonary fibrosis or carnification of the lung.

Abscess formation is rare. Multiple small abscesses are the rule, though occasionally a single large subpleural one with very irregular outlines is formed which may perforate into the pleural cavity and cause a pyopneumothorax.

Gangrene is also a rare accident of resolution. It results from necrosis of the lung, usually due to secondary infection with putrefactive bacteria.

Distribution of the Changes in the Lungs.—The right lower lobe is the site of the pneumonic process more often than the left, and both lower lobes are less often affected than one alone. When two lobes are involved, the disease usually affects both lower lobes, though it may involve two lobes of one lung or the upper lobe of one and the lower of the other, or both upper lobes. An entire lung may be involved and rarely the changes are limited to an apex. The unaffected lung is often congested and the portions of the diseased lung adjacent to the consolidated area may be edematous. The larger bronchi show congestion of the mucous membrane and contain frothy mucoid or serous material, and fibrinous casts of a bronchial tree may be found. The bronchial lymph glands are swollen and are often quite soft.

Lesions in Other Organs.—The most common finding, apart from those already described, is dilatation of the right side of the heart. The

right auricle and ventricle are usually filled with a tenacious clot, the like of which is rarely found in other diseases. There is cloudy swelling of the other viscera and in about half of the cases the spleen is appreciably enlarged.

HISTORICAL SUMMARY

Pneumonia was known to the ancients, and admirable descriptions of the disease are found in the writings of Hippocrates and Aretæus. The idea was general that all painless disorders of the chest were due to "peripneumonia," and it was not until the early eighteenth century that pneumonia and pleurisy were recognized as distinct maladies. This differentiation dates from the time when the study of pathological anatomy became a scientific practice, and more particularly from the time of Morgagni (1682-1771). Morgagni laid the real foundation of modern pathology, and it was he who recognized the manifestations of pneumonia to be the result of solidification of the lungs. Baillie (1761-1823) designated the pulmonary change "hepatization," and furnished the ground work for the epochal contributions of Auenbrugger (1722-1809) and of Laennec (1781-1826), whose observation led to the recognition of the disease by the use of methods of physical diagnosis and in turn made possible Rokitansky's differentiation between lobar and lobular pneumonia.

From this time until the late nineteenth century no great contribution was made except the elaboration of the physical signs and symptoms of the disease and the better recognition of the condition.

In 1874 von Jurgensen advanced the idea that pneumonia was an infectious disease due to a specific cause, basing his hypothesis largely upon the apparent incongruity between the local lesion and the severity of the systemic manifestations. Then came the era of bacteriology, the resolution of clinical complexes into etiological entities and the definite proof of the validity of Jurgensen's view.

Friedländer, in 1883, recovered an organism from pneumonic exudate with which he produced experimentally pleuropneumonia in mice and guinea-pigs. He termed this organism the "pneumococcus" but subsequently it was identified as an encapsulated bacillus and a very unusual cause of lobar pneumonia.

In 1880 Sternberg, Surgeon-General of the United States Army, and Pasteur independently described the organism generally responsible for lobar pneumonia, but neither recognized its specific pathogenic properties.

To A. Fränkel (1884) is due the credit of establishing the pneumococcus as the causal agent of lobar pneumonia. He isolated it from the sputum of pneumonic patients, noted its regular presence in the pulmonary exudate and, with pure cultures, infected mice, guinea-pigs and rabbits.

Fränkel's observations were confirmed shortly by Weichselbaum, who noted the occurrence of the pneumococcus in the blood and organs of a large series of cases in man; and subsequent routine examinations have completely established the validity of his observations.

With the further development of bacteriological investigation came the knowledge that lobar pneumonia may occasionally result from infection with Friedländer's bacillus or streptococci and rarely may be due to other organisms in the absence of the pneumococcus.

The succeeding twenty years brought refinements of the methods of diagnosis, the more general use of cultures of blood and sputum, immunological studies and futile efforts to discover a specific therapy. It was not until the beginning of this century that the path was blazed for the very modern procedures that are modifying our ideas of etiology and epidemiology of the disease and that are furnishing accurate prognostic data and a basis for a specific serum treatment.

Neufeld's subdivision of pneumococci into biological subgroups and the confirmation and extensive elaboration of his work by the workers at the Hospital of The Rockefeller Institute are of fundamental importance. Details of these observations are given in other sections of this article, but it should be stated here that, due to the discoveries of these investigators, the disease pneumonia is now better understood, knowledge of its mode of spread is more definite, prognosis is less problematical and the chances for the control and cure of it are greatly enhanced.

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CHAPTER VI

CEREBROSPINAL FEVER

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Definition, p. 83—Etiology, p. 84—Epidemiology, p. 84—Prevalence, p. 84—Predisposing causes, p. 85—Manner of spread, p. 86—Bacteriology, p. 87—Pathogenesis, p. 89—Symptomatology, p. 90—Clinical history, p. 90—Period of incubation, p. 90—Mode of onset, p. 91—Subjective symptoms, p. 92—Physical findings, p. 92—Special and laboratory findings, p. 97—Spinal puncture, p. 97—Examination of blood, p. 102—Nasopharyngeal cultures, p. 103—Differential diagnosis, p. 103—Complications and sequelæ, p. 105—Clinical types, p. 106—Meningitis in early infancy, p. 106—Posterior basic meningitis, p. 107—Mild cases, p. 107—Ordinary acute cases, p. 108—Subacute and chronic cases, p. 109—Hyperacute and fulminating cases, p. 109—Treatment, p. 110—Prophylaxis, p. 110—General management, p. 112—Symptomatic treatment, p. 112—Serum treatment, p. 113—Surgical indications, p. 115—Treatment of complications and sequelæ, p. 116—Convalescence, p. 117—Prognosis, p. 117—Pathological anatomy, p. 118—Historical summary, p. 119.

Definition.—Cerebrospinal fever is a febrile, infectious disease caused by the meningococcus, a Gram-negative diplococcus present in the nasopharynx of many well people, but also capable of invading the leptomeninges in sporadic cases and in epidemics, and of producing a purulent meningeal inflammation with the more or less characteristic symptoms and signs of the disease. These are commonly fever of comparatively sudden onset, headache, stiffness of the neck, vomiting, prostration, leukocytosis, generalized tenderness, photophobia, mental clouding, irregular respiration, herpes and an eruption most frequently hemorrhagic (not disappearing on pressure). The first three of these symptoms, fever, headache and stiffness of the neck, are usual, the others less uniform; many cases of the disease may be seen before one is found with an eruption other than herpes.

The disease has been called by other names: cerebrospinal meningitis, epidemic cerebrospinal meningitis, epidemic meningitis, typhoid meningitis, malignant meningitis, meningococcus meningitis, meningococcus sepsis, meningococcus infection, spotted fever, petechial fever, black fever, jail fever, hospital fever, brain fever, spinal fever, tetanoid fever and epidemic cephalalgia. The term cerebrospinal fever is preferred as indicating a disease entity, apart from any necessary anatomic localization, and at the same time emphasizing the usual site of attack. Thus it is coming to be recognized that the disease may occur without a menin-

gitis, yet with other symptoms and findings sufficient to establish its identity. This would invalidate the first six of the names in the above list. The term "epidemic meningitis," moreover, fails to take account of the ordinary sporadic cases. "Cerebrospinal meningitis" has been used by some in a broader sense, to include any inflammation of the cerebral and spinal meninges. "Meningococcus infection" and "meningococcus sepsis" are proposed by those who emphasize the systemic nature of the disease, yet these do not exclude such purely localized infections with the meningococcus as a conjunctivitis, an arthritis, or possibly a pharyngitis—infections which, though caused by the same microorganism, cannot be identified with the general disease. The other names are too indefinite and too little used at present to deserve more than the comment that their use should be entirely given up. The term "spotted fever" is especially obnoxious on account of its emphasis on an unusual symptom and its confusion with typhus, Rocky Mountain spotted fever, and with other eruptive diseases. Though still contending for a place with the infectious diseases in the International Classification of Causes of Death, the disease is listed as "Cerebrospinal Fever" in the 1918 American edition, and in the Bellevue Hospital Nomenclature, 1911 edition.

Etiology.—**EPIDEMIOLOGY.**—*Prevalence.*—In the absence of epidemics of cerebrospinal fever, the prevalence of the disease is to a considerable extent masked by confusion in diagnosis and in morbidity or mortality reports with other forms of meningitis. The non-epidemic incidence in American localities may be expected to be *less than 25 cases per 100,000* population per annum, with all cases accounted for, and outbreaks in large population centers do not usually go above five times this rate. Counting only a small group of inhabitants, such as a village or rural district, an outbreak may be so intense as to reach a 10 per cent. rate (10,000 per 100,000) per annum, but this is very rare.

Cases of cerebrospinal fever occur in all large communities throughout the year, but the characteristic seasonal prevalence is in *late winter and spring*, the epidemic and endemic peaks both occurring, as a rule, in January, February, March, April or May in the Northern Hemisphere, and in July, August, September, October or November in the Southern.

The disease is encountered both in the tropics and in the arctic regions, and records exist of outbreaks in all civilized countries, particularly in those of the north temperate zone. There have been *more epidemics* and a heavier sporadic incidence *in the United States than in any other nation*. This is especially striking if the European military epidemics be omitted from the calculation. It has long been noted that the assembling of troops in barracks gave rise to conditions which promoted the development of cerebrospinal fever, and many of the European outbreaks have been due to these conditions. The *English epidemics* of 1915, 1916 and 1917 were *primarily military*, for although considerably less than half of the 1915 cases occurred among soldiers, the civilian outbreak was by far more intense in those sections of the

country where troops were quartered than elsewhere. The French army in the active zone, out of about 2,500,000 men each year, had 1,073 cases in 1915, 451 in 1916, and 409 in 1917. The complete figures for the American army are not yet available, but the heaviest incidence was in the training camps in this country, particularly in Camp Jackson, Camp Beauregard, and Camp Funston, the annual rate for the first being about 1,500 per 100,000 per annum; for the second, about 750, and for the third, about 500.

Though the sharpest outbreaks of cerebrospinal fever are not in large cities, the *heaviest incidence*, both epidemic and sporadic, is in *urban communities* rather than in rural. It is thus somewhat more characteristically a disease of cities than is poliomyelitis, which it resembles in many other ways. The meningitis outbreaks may be diffused over a rather wide area, but they are more commonly sharply limited and without obvious radial spread from epidemic centers. Such spread as occurs is usually by leaps, and irregular.

The *greater prevalence among males than among females*, usually shown in statistics, is without special significance, since men are assembled in large groups, such as armies, which are particularly prone to be attacked, and since practically all diseases which have a predilection for the very young are more frequent and more fatal in males. A greater number of male than of female babies are born, but the former die much more rapidly (Nichols, 1907).

Cerebrospinal fever is an *infection of youth*. About half the cases may be expected to be five years of age or under; the disease is more fatal in infants than in older children, and it is not improbable that many cases are undiagnosed on account of the equivocal signs in the very young. Cases may occur in the eighth decade of life, or at birth (Koplik, 1916; Sedgwick, 1915; Dandy and Blackfan, 1917), and in some epidemics the incidence is heaviest during later childhood or early adult life. It is interesting to note, however, that even in an English military area, where the gross morbidity indicated that the soldiers were the most susceptible, when the number of cases was compared with the number of individuals of each age group living in the area, it was found that the incidence was heaviest among the very young children.

Predisposing Causes.—The influence of *age* and of the *assembling of large bodies of men*, as in barracks, has been noted. In regard to the latter, two considerations may be of importance: intimate contact, as assisting in the transference of infection, and the imposition of unaccustomed tasks, as tending to decrease the resistance of the individual. Outbreaks do not occur among young men assembled at the beginning of a college year, but here physical toil is not a factor. Though epidemics have occurred among resting veterans, a large proportion of the military outbreaks have followed actual *fatigue* (Hirsch, 1886), especially in the case of recruits. The question of *overcrowding* has been brought to the attention of the English particularly, and Glover (1918, 2) has advised that beds in cantonments be at least two and a half feet apart. In the American navy, the factors of fatigue and ex-

posure to cold have appeared to be of more importance than infection (Mink, 1918; Short, 1918) in determining the incidence of the disease in individuals. *Cold and damp weather* is thought to predispose to epidemics of meningitis, and attacks in some places have been said to have been preceded by "colds" or "influenza." It is certain that many outbreaks have not been correlated with particularly low temperatures or high humidities, and that no noteworthy rhinitis has preceded the greater number of cases.

An interesting observation has been made by Symmers (1918) that patients with *status lymphaticus* are prone to be attacked by a fatal form of cerebrospinal fever; 60 per cent. of the necropsies on cerebrospinal fever cases at Bellevue Hospital revealed *status lymphaticus*, while the incidence of the condition in necropsies on cases other than cerebrospinal fever was 8 per cent. The cases were fairly evenly divided among the different age groups. A similar predisposition was noted in Westenhoeffer's Silesian series of 29 necropsies.

Manner of Spread.—Cases of cerebrospinal fever usually occur, both sporadically and in epidemics, *without* demonstrable *direct contact* with other cases; spot maps show a scattered distribution throughout the localities affected. Doctors, nurses, or other patients do not ordinarily contract the disease from cases in hospitals. It is rare for more than one case to occur in a family, and instances of such occurrence are as likely to indicate simultaneous infection as infection of one case from another. In intense outbreaks familial and house distribution occurs; thus in Alexandria, Louisiana, eight cases and four deaths occurred in a family of nine, the father alone escaping. This was the neighboring town to Camp Beauregard, where a very fatal epidemic was in progress.

The explanation of this seemingly peculiar, but in fact not unusual distribution of an infectious disease, presumably spread by contact, lies in the evidence that *carriers* of the meningococcus are much more numerous than actual cases of the disease, and that the proportion of people who are ordinarily susceptible to the disease is very small.

Largely on the basis of German studies, it had been assumed that in the absence of epidemics, carriers were almost nil. English and American experience, and more recent German work, have indicated that even with material drawn from places where little or no cerebrospinal fever was occurring, the percentage of carriers might be 0.7 per cent. (Short, 1918), 1 per cent. (Bassett Smith, 1917), 2 per cent. (Mayer, Waldmann, Furst, and Gruber, 1910), 2 per cent. (Flack, 1917), 7 per cent. (Kutscher, 1906), 8 per cent. (Lewis, 1917), 10 per cent. (Griffith, 1916), 13 per cent. (Ponder, 1917), 14 per cent. (Scott, 1916), or even 25 per cent. (estimate of Fildes, 1918). Results are practically uniform that among "non-contacts" in epidemic areas, and particularly among "contacts"—i.e., persons who have recently been in close contact with actual cases of the disease—the proportion of carriers is higher than in persons from non-epidemic areas; it is also shown that the carrier rate generally rises at the season of the year when meningitis is

most likely to be prevalent, and that conditions of overcrowding increase the carrier rate.

The actual manner of spread is therefore assumed to be usually by droplet infection from carrier to carrier, and finally to a susceptible individual who develops the disease.

BACTERIOLOGY.—Morphology.—The meningococcus, called at first *Diplococcus intracellularis meningitidis*, is an organism easily stained by the ordinary basic aniline dyes, but losing the stain when decolorized by Gram's method, and taking the counterstain instead. It disintegrates or autolyses very easily and except in smears from fresh young cultures may be seen in a variety of sizes and intensities of staining reaction; its Gram-negative nature is constant, when the staining and decolorization are properly performed, and serves to distinguish it from all other intact organisms (except Pfeiffer's influenza bacillus) which are commonly found as causes of meningitis. Other cocci, properly Gram-positive in young cultures, may show Gram-negative forms when older or when injured in any way. A satisfactory method of applying Gram's stain is to stain the smear with active carbol gentian- or methyl-violet for three minutes without heat, pour off the stain, apply the iodine-potassium iodide solution for one minute, pour off, or blot, decolorize by allowing successive drops of absolute alcohol to flow over the slide till the color comes out—this should not require more than two minutes with a thin smear—wash in water, and counterstain for only fifteen seconds with safranin or with a one-in-ten dilution of carbol-fuchsin. It is well occasionally to control this stain by smears, on the same slide, of a known Gram-positive organism such as the diphtheria bacillus from an 18 to 24-hour culture at one end of the slide, and a known Gram-negative organism such as the typhoid or colon bacillus at the other.

Meningococci in fresh cultures are medium-sized oblong or kidney-shaped cocci, arranged in pairs with the broad side of each coccus facing the other coccus of the pair. Tetrads are frequently seen, but chains are unusual. In smears from the spinal exudate and from other sites of pathological invasion, the cocci are commonly, but by no means uniformly, found within polynuclear leukocytes. The predominance of free cocci is taken as a bad sign, since as cases progress toward improvement, the cocci become entirely intercellular.

Cultures.—In cultures the meningococcus, like the gonococcus which it resembles, prefers the enrichment of the medium with some animal fluid, and when first isolated will hardly grow without such enrichment. The media proposed, some containing serum or blood, and some without, have been very numerous. Growth on ascitic agar is usually prompt, the larger colonies reaching two millimeters or more in diameter in twenty-four hours, and presenting a rounded, moist appearance with smooth, well-defined edges; the color is a translucent gray at first, becoming whitish or slightly yellowish or brownish as the growth becomes more profuse, but showing no pronounced color with age; this cultural appearance is not always present (Conti, 1918). Moistness and

freshness of the medium, with maintenance of a constant temperature, are requisites of success in growing meningococci. The organisms will not usually survive drying out, or any considerable fluctuations in temperature. Absence of growth at 23° C. has been held as one of the criteria for identifying the meningococcus. Ordinarily the meningococcus must be rather frequently transplanted to survive prolonged cultivation.

Typically the coccus ferments glucose and maltose but not saccharose, and this, together with its cultural characteristics as given above, serves to differentiate it from other Gram-negative cocci as a rule. The variation in intensity of these fermentations, together with variations in the media used, adds an element of uncertainty to such differentiation: provided the sugars are pure, the variation is in the direction of diminished fermentative power, rather than of increased.

Serology.—Serologically meningococci do not behave entirely as a unit, but show differences among themselves and resemblances to such allied organisms as the gonococcus. By agglutination Elser and Huntoon (1909) found marked differences in degrees of reaction, some strains being relatively inagglutinable. Arkwright (1909), from twenty-five epidemic and twenty sporadic strains, made more than three groups and subgroups. Dopter's parameningococcus (1909, 3) was the first generally recognized variant, and Dopter and Parron (1914) have since noted two other variants, calling the four groups meningococcus, parameningococcus alpha, parameningococcus beta, and parameningococcus gamma. The term "parameningococcus" is an unfortunate one, since any of the varieties given that name might as justly be called meningococcus as the original strain. Ellis (1915), of the Canadian forces in France, found two broad agglutinative groups, and a similar grouping is found by the workers of the English Local Government Board (Eastwood; Griffith; Scott, 1916 and 1917; Ponder, 1917), though as many as five or six subgroups might be recognized within a single broad group. In the hands of almost all workers, by far the greater part of the strains examined correspond more or less closely to one of two types. By the use of rapidly prepared monovalent rabbit serum for agglutination, and also by the absorption of agglutinins, Gordon and his co-workers in and from the Central Cerebrospinal Fever Laboratory of the Royal Army Medical College differentiated types I, II, III and IV as responsible for practically all of the meningitis among the English forces during 1915 and 1916. Using rapid agglutination at room temperature instead of the standard method of agglutination at 55° C. overnight, Nicolle, Debains and Jouan (1918) divided their strains into groups A, B, C and D, which they said corresponded, but not exactly, with Dopter's meningococcus, and paras alpha, beta and gamma respectively; they also found Gordon's types I and III falling in their A group, and II and IV in the B group. Correlations of these various European groupings among themselves and with the common American division (Amoss, 1917) into normal or regular, irregular and para strains have not been uniform and satisfactory, so that it is not possible to say that a given group in one system corresponds fully and completely with any group

in another system. There are many cross relations and overlappings between groups; complement-fixation has in general given broader, less sharply specific reactions than has agglutination. A sharper degree of subdivision is possible by absorption of agglutinins than in any other way, but the practical significance of such subdivision may be questioned.

It has been shown that meningococci may be classified on the basis of their reaction to phagocytosis with specific sera.

The tropin group R corresponds roughly with Gordon's agglutinative types I and III, tropin group S with agglutinative Type II, and there are at least three other tropin groups, T, U and Z. There is some indication that the prevalent types are changing so that the sera for intraspinal therapy should be maintained representative of the various types encountered. This is done for American sera.

These considerations are of importance as regards the definition of the meningococcus when a Gram-negative diplococcus similar to the meningococcus is found in the nasopharynx, and as regards the polyvalency of serum to be used in the treatment of the disease (McCoy, 1918). American sera are required to have a broadness of action sufficient to cover all strains ordinarily encountered.

Experimental Research.—Some points in the proof that the meningococcus is the cause of cerebrospinal fever are lacking, but the evidence is so overwhelming as to be conclusive. The attempt by Hort to incriminate a filterable virus, although recent, has now only the historical interest which attaches to the former confusion of the pneumococcus with the meningococcus, and to the assignment by Jaeger and others of an etiological rôle to other, Gram-positive, cocci which we now look upon as contaminations. Though the meningococci are sometimes not to be found, the uniformity of the presence of cocci answering the description of meningococci in the spinal fluid of epidemic cases is too great to explain on any other grounds than that they actually cause the disease. Meningococci are irregularly pathogenic when injected intraperitoneally into certain animals, particularly young guinea pigs and white mice. Subdural injections have caused meningitis in rabbits, dogs, a goat, and monkeys, but such direct inoculation does not prove the elective localization which the meningococcus must show in human infection. Intraspinal inoculation of monkeys enabled Flexner to follow the action of antimeningococcal serum and gave a great stimulus to the use of the latter in human cases. Austrian (1918) succeeded in producing a typical fatal meningitis in three out of twenty rabbits inoculated intravenously with meningococci by giving a simultaneous intraspinal injection of normal rabbit serum. Weed, Wegforth, Ayer and Felton (1919) have similarly caused the meningeal localization of *Bacillus mucosus capsulatus* injected into rabbits intravenously, merely by withdrawing spinal fluid through a lumbar puncture.

PATHOGENESIS.—There is no reason to doubt that the meningococcus reaches the body, and leaves the body, by way of the nasopharynx, where it is commonly found. That the meninges are invaded by direct extension through the ethmoid or sphenoid, as urged by Weigert and by Westenhöffer, is open to serious question. The regions of favorite locali-

zation at the base of the brain are not actually in relation with the nasopharyngeal sinuses, though thought at first to be so, and there is no communication between the lymphatics of these sinuses and the cerebrospinal system. The subarachnoid space with the ventricles and the perivascular and perineural spaces of the brain and cord form a closed sac, and lymph spaces are not found; cerebrospinal fluid takes the place of lymph within that part of the central nervous system which is enclosed by the dura mater. The experiments just related of Austrian, and of Weed, Wegeforth, Ayer and Felton suggest that the meninges are invaded by way of the blood, and this coincides with the occasional positive blood cultures early in the disease. It must be stated that the meningococci apparently do not as a rule multiply in the blood stream so as to constitute a true septicemia, but that they quickly seek their natural pathogenic habitat, the meninges, though other sites of lessened specific resistance are occasionally found. That the meningococcus has a relatively low pathogenetic intensity is shown by the fact that it is the only known pathogenic bacterium which can infect the meninges without producing practically 100 per cent. fatality.

It has been frequently held that the harmful effects of the meningococcus are due to "endotoxins," or poisonous bodies bound up with the bacteria themselves. Certainly autolysates, and various products formed by the disintegration of the microorganisms, may be very toxic. Whether the bodily defenses which overcome the disease are chiefly directed against such toxic products or against the living cocci is not known. Of the antibacterial forces, those known as bacteriotropins or opsonins, which promote the phagocytosis observed to be coincident with recovery, are of prime importance. There is no doubt that the factors of individual resistance or susceptibility weigh more heavily in determining whether or not an attack will take place than does the matter of chance infection.

Symptomatology.—**CLINICAL HISTORY.**—*Period of Incubation.*—Our former ideas of a more or less definite period of incubation for each infectious disease have undergone some modification of late. In general, the more highly contagious the disease, the more definite the period of incubation, and cerebrospinal fever being of a low degree of infectivity, its period of incubation is variable and uncertain. The experience with military tetanus, for example, has demonstrated that the infecting organism may long lie dormant in a healed wound, to be stirred into activity by a subsequent operation or even by therapeutic exercises. So it is believed in some quarters that every case of cerebrospinal fever is first a carrier of the meningococcus in his nasopharynx, and that by a breaking down, perhaps temporary, of the barrier of defense, the coccus is enabled to invade the body and cause the disease. Flack (1917) reports 5 cases in the London district developing among carriers in from one to forty days after their isolation. Short (1918) reports 6 cases out of 1,228 carriers at Great Lakes Station. On the other hand, among 485 carriers in the British Navy at Portsmouth kept under observation by Fildes (1918) during an outbreak, not one developed meningitis. A similar absence of meningitis among carriers was found by Robey (1918), Redden (1918) and Landry (1919). On the rare occasion of more than one case occurring in the same family or among messmates, the cases may be separated by hours or months. The possibility of both cases being infected from a common source is to be borne in mind. More definite are the cases which develop in a previously non-infected district

after a visit to or from an infected focus. Such evidence places the usual incubation period at from *one to five days*. The former corresponds to the case reported by Sophian (1913), apparently contracted at the necropsy on a malignant case; it is reasonable to suppose that a disease which can run such a rapidly disastrous course as the fulminating type of cerebrospinal fever may at times have a very short incubation period.

Mode of Onset.—The onset as a rule is *sudden*; the patient has enough fever and prostration to be kept in bed within twenty-four hours of the first clear symptoms. Premonitory indispositions occur, but one cannot say whether these are a part of the disease itself, or a lowering of resistance, due to another cause, and opening the way for a meningococcal infection. Ambulatory cases with a true meningeal headache are unusual. Koplik has described cases with intermittent onset and course. Intervals of entire remission of symptoms early in the course of the disease are not common in the experience of most observers, although the French writers and Foster and Gaskell have emphasized a lack of increase of symptoms or a clinical improvement in many of their cases on the second day, even without treatment. A normal temperature may be maintained for several days, and delay the diagnostic puncture. The temperature charts during the later course of the disease are often irregular, but the patients do not regain entire well-being in the afebrile periods.

An early catarrhal stage of the disease has been described in some epidemics, notably at Aldershot in England. Surveys of the nasal and pharyngeal condition at the onset, as well as in carriers, have not tended to substantiate the idea that an initial rhinitis or pharyngitis is notably more frequent or pronounced than in other fevers, nor that the meningococcus necessarily, or even commonly, sets up an inflammation in the throat. The conditions of overcrowding, stress and bad weather which frequently accompany epidemics of meningitis are apt to breed coryzas and similar infections.

A *chill* with rigor, or a convulsion in an infant, frequently ushers in the disease. The chill may be replaced by chilly feelings and malaise, or this period of invasion may be so masked or so soon succeeded by definite meningeal symptoms or unconsciousness as to escape notice. The convulsions are not usually prolonged beyond the first few days, and are very rare in adults.

Vomiting occurs in more than half of the cases at, or soon after, the onset. Though this symptom together with a not uncommon abdominal pain in children, often directs attention to the gastro-intestinal tract, the vomiting usually is not preceded by nausea and frequently bears no relation to meals. Vomiting is a symptom of the initial stages, and is not usual thereafter, in contrast to other cerebral diseases. In a disease with the severity of cerebrospinal fever it is to be expected that the appetite will be lost or very largely impaired; nutrition is therefore an important part of the treatment, particularly when the course is prolonged. Evidence of malnutrition may be seen as early as the fourth

or fifth day, especially in hydrocephalic cases, which characteristically have abdominal retraction. Sleeplessness promotes the catabolism of the patients' tissues with resultant loss in weight. As a rule, the vomiting is not sufficiently prolonged to be a factor of much importance in this respect.

Subjective Symptoms.—Usually the first definitely meningeal symptom in an adult is *headache*. This may be referred to any or all parts of the cranium, frontal headache frequently giving way to occipital as the disease progresses. Not at first differentiated from an ordinary headache accompanying any general infection or toxemia, the headache of cerebrospinal fever typically becomes in intensity one of the most prominent symptoms unless supplanted by delirium or mental dullness or unless relieved by treatment. It is not stopped by ordinary methods, such as cool applications and mild analgesics; if the patient knows by experience the improvement following lumbar puncture he may beg for the latter, although it is to be performed without anesthesia. The fact that this characteristic symptom is definitely absent in some cases leads us to expect it to be mild in others, and to resort to lumbar puncture even if the headache is not present in its typical severity, provided other sufficiently significant indications are found.

The mentality at onset and in the early stages may be normal, with allowance for the prostration, pain and natural apprehension. Commonly the patient is either hypersensitive and irritable, or dull and unresponsive, though in the epidemic cases there may be delirium, stupor or collapse when first seen. During the height of the disease a case of average severity may be expected to be deeply stuporous with some delirium but without complete coma. A disordered mental condition persists at times well into convalescence. Vertigo or double vision is an occasional complaint.

The bowels are usually constipated. In Goeppert's series diarrhea was not uncommon.

PHYSICAL FINDINGS.—The most important sign of meningitis is *stiffness of the neck* or resistance to flexion. In eliciting this sign the examiner should proceed with all gentleness, especially in the case of children. It is well to secure the history and make other less important and less painful examinations first, in order to gain the confidence of the patient. Rotation of the head from side to side should be attempted, though lateral rigidity is not so significant as anteroposterior. To determine the latter with the patient lying on his back, the hand of the examiner should be inserted between the occiput and the pillow, palm upward, and gently raised. In meningeal conditions this causes pain, and instead of the chin approaching the sternum, there is a tendency for the shoulders to rise from the bed. Unless the condition is marked, one examination is not sufficient, but another attempt to flex the head should be made at the conclusion of the other tests. Unlike a rigidity of less serious import, the neck rigidity of meningitis does not loosen up on manipulation. Netter advises that the naked patient be placed supine on a flat table to detect any spastic arching of the cervical spine.

Though in health the chin should be able to touch or nearly touch the sternum, it is necessary to test for this sign in many non-meningeal cases to appreciate the degrees of voluntary or unconscious non-pathogenic resistance which may be encountered at different ages and in different patients. In general, by repeated trials at different times one is able to distinguish a true from a false stiffness; but in the early stages of meningitis this may be a fleeting symptom, absent at times. Even with fully developed meningitis, limited to the convexity of the skull (Holt), or in the very young (Koplik), or in patients profoundly prostrated and collapsed, there may be no stiffness. In ordinary cases of meningitis, the rigidity may not be found before the end of the first week, though this is unusual. Needless to say, in cases with general meningococcus septicemia without meningitis or before meningitis has begun, the sign is lacking. Aside from local conditions giving rise to stiffness, such as abscess or neuritis, easily distinguished by the absence of general symptoms, other causes of neck rigidity, particularly meningism, are discussed under Differential Diagnosis. Attempted flexion of the neck in meningitis is usually painful. This is probably the reason for the dilation of the pupils which may frequently be observed when flexion is attempted. The neck sign of Brudzinski is elicited at the same time by flexing the head with one hand, the other exerting counter pressure on the chest to prevent the shoulders from rising; in response to this maneuver in meningitis, the thighs usually flex on the abdomen, and the legs flex at the knees, often with some eversion.

The stiffness of the neck may be so marked that some retraction (opisthotonos) is visible. In the typical developed case of meningitis the posture is on the side so that the head can be more fully extended than when lying on the back. This posture may give a hint of the disease, although a considerable amount of flexion is actually possible on trial. Flexing the back by placing the examiner's arm under the patient's knees and raising them, the patient being on his back, is also likely to demonstrate some painful rigidity. The most marked opisthotonos and retraction of the head is seen in the chronic stages of meningitis, and particularly in the form known as posterior basic meningitis of infants and children.

Of almost equal import with the information obtained by attempting to bend the neck forward, is the phenomenon known as *Kernig's sign*; this is a resistance to passive simultaneous flexion of the hip and extension of the knee. It is best elicited by Osler's method: the patient being flat on his back, the lower leg is raised by the examiner, keeping the tibia horizontal till the femur is vertical; an attempt is now made to straighten out the knee and raise the tibia to a vertical position, the angle of 90 degrees being maintained at the hip. Any limitation of extension to an angle of 135 degrees or less at the knee may be considered as a positive Kernig's sign. In the elderly a positive Kernig's sign is normal and not indicative of disease. In children under two years of age the sign is variable, but with this as with many other reflex phenomena, repeated examination, after having gained the confidence

of the infant, will often give information of value. The resistance to extension in a positive Kernig's sign is involuntary and mechanical, due to a hypertonicity of the hamstring muscles, and also voluntary, on account of the pain caused by extension. The sign is at times observed in hip disease and spinal caries, as well as in meningitis and meningismus. Brudzinski's identical and reciprocal contralateral reflexes, a flexion (identical) or extension (reciprocal) of one leg when the other is passively flexed, are frequently present in meningitis, but are not as important as his neck sign.

Other pathological reflexes such as Babinski's and Oppenheim's give no help in meningitis. They may be present, but are usually absent.

A general examination of all the ordinary reflexes is to be recommended, not only for the diagnosis of meningitis, but also for that of poliomyelitis, which often bears a decided resemblance to cerebrospinal fever in the early stages. In general, it is to be expected that the *deep reflexes* will be somewhat *exaggerated at the onset* of meningeal involvement, and the *superficial reflexes dulled*, but changes in the opposite direction may occur, the deep reflexes being usually lost later in the disease. In children, they being the most susceptible to cerebrospinal fever and acute poliomyelitis, one can normally obtain knee, ankle and biceps jerks. The principal superficial reflexes are the abdominal, obtained by stroking either side of the abdomen with a pin or a splintered wooden tongue depressor; the epigastric, a drawing in of the epigastrium when the skin below either nipple is stroked; the lumbar, a contraction of the lumbar muscles in response to a stroking of the skin of the back below the ribs; the gluteal, a similar contraction of the gluteal muscles when the transverse fold of the buttocks is stroked; the cremasteric, obtained by stroking the inner thigh; and the plantar, a flexion of the toes when the sole is stroked, usually accompanied by flexion of the knee and hip. Reflexes are so variable and so subject to volitional control by the patient that any deviation from the normal which is found should be substantiated at a reëxamination. In examining the superficial reflexes, the *tache cérébrale*, a persisting red line with white borders, may be brought out by the stroking, but it is of too frequent occurrence in other febrile disorders to be of any diagnostic value.

A more important sign of meningitis, however, is brought out by the general examination of the reflexes. This is *tenderness*, general hyperesthesia of the skin and deeper structures, which is usually present and significant, if the meningitis is at all severe, and if the patient is conscious. Formerly spinal tenderness was considered as of special importance, but it is now recognized that any or all of the sensory nerves are likely to share in this over-acuteness of conduction. The symptom is commonly attributed to inflammation around the dorsal nerve roots, and to increased tension of the cerebrospinal fluid. Secondary effects of this are the restlessness, apprehension and irritability which the patient shows, a disinclination to be handled or moved. Sophian has called attention to a tenderness at the angle of the jaw in many of the cases.

Corresponding to this exquisite sensitiveness and to the frequent changes in reflexes is a general *stiffness* of the muscles, a hypertonicity often not very definite, but suggestive.

The *photophobia* which is so common in the disease and the sensitiveness to sound are probably likewise due to the afferent nerves being "on edge."

The *pain*, which is primarily cranial, may spread to the neck, back, abdomen, and become generalized. It may be so severe as to make the patient cry out, and frequently contributes to an early delirium.

Sleeplessness from pain, as well as photophobia, may cause a *suffusion of the conjunctivæ*.

Tremor is not uncommon, particularly a coarse intention tremor in children, together with nystagmus.

Actual paralyses are unusual, though strabismus, ptosis and transient face palsies occur in children.

Increased intracranial pressure is not as rapid in development as the other evidences of the disease, but gives rise to a train of signs of which the *tense or bulging fontanel* of infants is the most obvious. Corresponding to this sign in older children and adults is *MacEwen's sign*, a heightened resonance of the percussion note over the lateral ventricles of the brain (MacEwen, 1893; Wilcox, 1915; Koplik, 1915; Regan, 1918). Though there is disagreement concerning the technic of this sign, a good method of eliciting it is as follows: With the patient's head held on one side, percussion is made by the finger directly on the dependent parietal eminence, or on a point about two inches above and behind the external canthus of the lower eye. When the position of the head is reversed, the opposite parietal region gives the clearer note. To appreciate the increased resonance of a positive MacEwen's, it is necessary to carry in mind the variations due to the thickness of the skull at different ages. Rachitic children may give a clear note also, without increased cerebrospinal fluid. In adults the sign is not as clear, but bony conduction may be eliminated by auscultating the forehead just above the nose while the percussing finger is brought gradually forward from the parietal eminence; if there is increased intracranial tension the note should become less clear as the percussion approaches the stethoscope.

Ophthalmoscopic examination has not given much evidence of value in most epidemics of meningitis. Congestion of the disk is more common than choked disk or optic neuritis.

The *pupils* are usually dilated and react sluggishly. They may be unequal or contracted at first. Hippus, an alternating contraction and dilation independent of accommodation, is sometimes observed.

Deafness is not infrequent in the disease and is often central in origin, as is the blindness which occurs in infants.

The tongue is often dry and tremulous and later becomes covered with sordes. It is very possible that the redness of the throat which has been attributed by some observers to a specific meningococcus pharyngitis is, like the dry tongue, merely a part of the general febrile dis-

turbance. At any rate, sore throat is not a characteristic complaint in cerebrospinal fever.

Retention of urine, probably spastic in nature, is frequent and should be watched for from the first as cystitis and pyelitis are easily induced. Incontinence and dysphagia occur. Polyuria is not infrequent, but albuminuria and glycosuria are no more common than in other fevers. Acute nephritis occurred in 9 out of 161 cases reported by Bourke, Abrahams and Rowland (1915) of the British Expeditionary Force.

The *temperature* of cerebrospinal fever at the onset is typically high, but there is nothing constant or diagnostic in the chart, though *irregularity* is very common. The temperature is a poor guide to the condition or prognosis of the patient.

The pulse is often rather slow in proportion to the temperature, and shows variations independent of the fever. Bradycardia and irregularity are not as characteristic of this disease, however, as of tuberculous meningitis. The blood pressure as a rule is high, especially with increasing intracranial tension; conversely a low blood pressure during the first sixty hours of the disease indicates a dangerous collapse (Fairley and Stewart, 1916).

The respiration in the early stages may not be abnormal, but with fully-developed meningitis, particularly in the later stages and in the severe cases, it is likely to exhibit irregularity (Connor and Stillman, 1912). In children the Cheyne-Stokes type of breathing, with regularly recurring periods of apnea and hyperapnea, is particularly suggestive of meningitis. But the two types most significant are the undulatory irregularity without entire apnea, and Biot's breathing. The latter is of grave prognostic omen. It is characterized by irregular periods of apnea, by constant irregularity in the rhythm and depth of breathing, and by frequent sighing respirations. The respiratory phenomena and slow, hard pulse are both probably due to increased tension of the cerebrospinal fluid, and to the same cause is attributed the fact that death is usually from respiratory failure.

Further examination of the internal organs gives, as a rule, no results of consequence. The spleen is frequently enlarged as in other fevers. Cardiac and pulmonary complications are more often found post-mortem than antemortem. The presence of another disease—bronchitis, pneumonia, typhoid fever—by no means excludes meningococcal infection. Jaundice develops in a few cases.

The most frequent skin manifestation of cerebrospinal fever is *herpes*, commonly about the mouth or nose. It does not usually appear before the 3rd day, and is rare in infants under two years of age. In some outbreaks it is rare in any case, but its appearance is a point in favor of this disease as against the other conditions, except pneumonia, which simulate cerebrospinal fever. Herpes has no prognostic significance.

The typical *eruption* of the disease is a hemorrhagic one, the spots varying in size from flea bites to enormous blotches in different cases, and showing much variation in the individual case. This eruption is

unusual in sporadic cases, and in many epidemics it is observed in less than 50 per cent. of the cases. Cases with eruption are, on the average, somewhat more severe than those without, but the difference in mortality between the two classes is not constant. The petechial and purpuric blotches appear from the first to the third day, occur on any part of the body, and may be associated with other hemorrhages, bloody bullæ (subcuticular hemorrhages) have been described. Of somewhat later and less frequent occurrence are the eruptions which simulate to some extent those of typhoid, measles or scarlatina. Individual spots will often be found here also to be hemorrhagic. Eruptions, either erythematous or hemorrhagic, are especially frequent over pressure points, such as the elbows and the trochanters. Local flushing alternating with pallor, and localized sweats are part of the vasomotor phenomena. A serum rash, usually urticaria, may be expected in a small percentage of treated cases, but does not commonly appear less than a week after the injection which provokes it.

SPECIAL AND LABORATORY FINDINGS.—1. *Spinal Puncture*.—(a) *Indications and Contra-indications*.—The one necessary measure for diagnosis and treatment in cerebrospinal fever is lumbar puncture. On serious suspicion that a case might be one of meningitis, puncture should be performed at once, with serum at hand for administration at the first puncture; each day's delay increases the chances of a fatal termination. But lumbar puncture is not as simple, painless or harmless a procedure as taking a throat culture for diphtheria. What, then, are the indications for its performance?

In the presence of an epidemic, puncture should be done on slighter provocation than in non-epidemic times, both because indefinite illnesses are more likely to be meningitis, and because the cases that occur are more severe and consequently more in need of instant treatment. If cerebrospinal fever is present in the community in more than sporadic intensity—more than one case per week per 100,000 population—all patients with fever of severe sudden onset, headache and vomiting should be punctured. Stiffness of the neck, or Kernig's sign, or delirium, or stupor, or an intense headache, or an eruption which does not disappear on pressure, even though the petechiæ be few in number, is enough to justify the operation, if explanation other than meningitis is not evident. Blood-cultures and nasal cultures should also be made.

The more punctures that are done in a community under those conditions, the lower will be the mortality. In the absence of an epidemic one usually waits for definite signs of increased tension of the cerebrospinal fluid, such as a neck sign or Kernig's sign, in addition to other suggestive findings, before puncturing.

As soon as there is a fair possibility that the symptoms are caused by a purulent meningitis, puncture should be performed. But if the meningeal symptoms are only slight, and the probability is strong that they are due to meningism or poliomyelitis, puncture may be postponed until definite benefit by the relief of pressure may be expected from the operation. The mistake must not be made of refraining from

tapping because the first attempt gave negative results, if the symptoms pointing to the meninges continue and increase; the cerebrospinal fluid frequently appears sterile during the early stages of cerebrospinal fever.

The indications in the case of new born and very young infants are different because of the absence of localizing symptoms (Koplik, 1916). It is probable that many cases of meningitis are missed here which either prove fatal early or develop a hydrocephalus. Convulsions with fever not necessarily continuous, restlessness without intestinal disorders, twitching, regurgitation not preceded by feeding, constitute a train of symptoms which justify puncture.

The contra-indications to lumbar puncture are nil, if indications are present and the operation can be performed aseptically. The meningitis division of the New York City Health Department laboratories has performed over 3,000 lumbar punctures, often under the poorest local conditions, without a single secondary infection of the meninges. While there are no contra-indications, the procedure is not to be undertaken lightly in the absence of a reasonable chance that the patient will be benefited. The puncture is somewhat painful and is not without a slight element of danger. Koplik records two sudden deaths on the withdrawal of a small amount of purulent fluid from infants; Flexner and Amoss have shown that an accidental puncture of a meningeal vein may experimentally localize a poliomyelitis virus which would otherwise remain in the blood stream without harm. Weed, Wegforth, Ayer and Felton (1919) have demonstrated a similar production of bacillary meningitis by lumbar puncture in the presence of an experimental septicemia.

(b) *Anatomy and Technic of Spinal Puncture.*—The lower end of the spinal cord in adults is practically always above the third lumbar vertebra and may be as high as the twelfth dorsal. At birth the average level is the third lumbar. The space between the fourth and fifth lumbar vertebrae is therefore always safe for puncture without danger of injuring the cord, and the next space above or below this one can be used. This point of election corresponds usually to the space nearest the line joining the crests of the ilia. It is convenient to mark these crests with tincture of iodine and to paint a narrow transverse line on the patient's back at this level before beginning the puncture. If the back is held properly flexed, the cord is drawn still higher within the vertebral canal, so that one or two interspaces above the three mentioned are safe in adults. The spinous processes of the lumbar vertebrae are practically horizontal, and between the bases of these processes is enclosed a diamond-shaped opening, which is our entrance to the meninges. If the puncture is made in the midline, perpendicular to the plane of the back, as is advisable, the needle will puncture first the skin and subcutaneous tissue, next the tough supraspinous ligament, then the more easily separated intraspinal ligament, then the dura, which is the last resistance to be felt. The total distance traversed varies from one to four inches with the age and with the osseous and subcutaneous development. The subdural space and the arachnoid membrane are negligible; the subarachnoid network containing the cerebrospinal fluid lies practically under

the dura. The nerve-roots of the cauda equina are of some importance in lumbar puncture, as they may be slightly irritated or injured, causing symptoms in the lower extremities, bladder or anus. Also, some of the filaments may temporarily cover the open end of the needle, preventing outflow. When the dural resistance has been felt to be overcome, the needle should be pushed no farther, both to avoid any injury to the cauda, and to avoid striking the plexus of blood-vessels in the anterior part of the canal. This plexus is most developed in the dorsal hollows of the vertebral bodies, so that if the needle is in the intraspinal space at an angle of 90 degrees, the point would strike the upper edge of the vertebral body, rather than the vessels. The tips of the vertebral spinous processes are rounded, and in the adult have a tubercle on their lower surface. The needle should therefore be inserted fairly between these palpable tips, but should follow the lower process rather than the spine above. At times the point of the needle will strike the lower spine in this fashion, due to a slight downward inclination of the spinous processes from before backward. This is particularly true if the spine is not well flexed, and may be overcome by directing the needle upward (toward the head) at an angle of not less than 45 degrees. Flexion of the spine does not change the direction of the spinous processes appreciably, but separates them.

If puncture at the first site is to be abandoned on account of non-success or local irritation of the skin, another interspace may be selected, or the lateral method may be tried, the needle being inserted one-half to three inches from the median line and pointed mesially, upward and inward. If only slightly to one side of the midline, the same diamond-shaped opening may be entered as with median puncture, while farther out the needle punctures the subflavian ligament and passes between the sloping laminae. The disadvantages of lateral puncture are, that the direction is bound to be uncertain on account of the varying thickness of the overlying structures, that the vascular muscle must be pierced, and that the needle tract is longer.

The two most essential points in lumbar puncture are asepsis and the proper holding of the patient. There is more art in the latter than in the performance of the puncture.

No anesthesia is usually employed. A general anesthetic is unwise except for a violently struggling patient, and the possible devitalization of the skin with consequent infection from local anesthesia outweighs its advantage, since lumbar puncture usually is repeated a number of times. Deftness of operation, a due regard for the comfort of the patient, and some mental distraction suffice, and are the safest aids.

Antimeningococcic serum should be at hand for immediate injection without withdrawing the needle in case the cerebrospinal fluid is cloudy at the first puncture. The sterile needles and outfits for gravity administration, which are furnished in commercial packages of the serum, are as a rule very satisfactory. For very young infants a smaller, sharper needle with a syringe for aspiration is sometimes an advantage, but aspiration must be very gently performed, as it is apt to cause

bleeding. In infants the prolongation of the thecal sac below the end of the spinal cord is smaller than in older persons. If the pus is very thick or flaky, a needle of larger caliber may be used. If no outfit for administration is furnished with the serum, one may be extemporized by opening and drawing out the lower end of a test-tube so that a rubber tubing about $3/16$ of an inch in caliber and 14 inches long may be slipped over it and may be connected at the other extremity with the needle. A bit of glass tubing should be inserted in the rubber tubing near the needle. The needle should be about $4\frac{1}{2}$ inches long and $1/16$ of an inch in diameter, with obturator. The bevel of the needle should be as abrupt as is consistent with a sharp point; that is, the distance from the extreme point across the opening at the end of the needle should be as short as possible—not over $1/8$ of an inch. The needle, tubing, and test-tube funnel are sterilized by boiling for five minutes. A basin of mercuric bichlorid solution, 1:1000, at a temperature of about 105° F. (40.6° C.), is used for warming the serum.

It is usually advised that the fluid be caught in a series of sterile test-tubes. The author has found bottles preferable, except in cases where but little fluid is to be expected, using short, wide-mouthed, glass-stoppered bottles, of clear glass, about an inch and a half in diameter, and holding one ounce (30 c.c.), the first spurts of the fluid being caught in one and the remainder in others, so that any turbidity due to accidental bleeding will not be present in the last sample. These bottles are sterilized with tin foil or paper caps, can be set down on the edge of the bed or on an uneven floor with little danger of spilling, and are readily transportable. They can be held under the needle in the middle of the bed, if necessary. Theoretically the patient should be brought to the edge of the bed, and the rubber tube be connected with the needle as soon as the fluid begins to flow, but this is not always practical. With these bottles, faint cloudiness of the fluid is more easily detected than in narrow test-tubes—an important point for rapid diagnosis. The amount of fluid withdrawn is likewise readily estimated, and in convenient units, since 30 c.c. is the usual amount of serum in one package.

Sterile gauze and sterile towels should be at hand. The patient's back is cleansed with alcohol, wiped dry with sterile gauze, and the puncture area painted with iodine. The hands of the operator are prepared as for a surgical operation; breaks in asepsis are particularly disastrous because any infection of the spinal canal with pyogenic organisms, other than the meningococcus, is practically always fatal. John L. Morse wears a sterile finger cot over the left forefinger for palpating the intervertebral space to be punctured. One advantage in sterile rubber gloves lies in diminishing the chance of contaminating the hub of the needle over which some of the spinal fluid must flow; every effort should be made to keep the fluid uncontaminated for bacteriological cultures. With care this can be managed by pressing the palm against the head of the obturator and holding the needle with the fingers a short distance away from the hub, or by allowing the fluid to flow through the sterile rubber connection.

Puncture of a febrile patient should not be done in an upright position. The patient should be held by an assistant with the lumbar spine even with the edge of the bed. For successive punctures the patient may lie on alternate sides, although the left side is usually more convenient for the operator. With one arm over the patient's shoulders, the other around the patient's flexed knees, and hands tightly clasped beneath to maintain this posture, the assistant can keep the patient's spine well flexed. A rope made of a sheet may at times serve the same purpose, the assistant's knee being placed against the patient's abdomen to maintain the flexion.

The needle is inserted as previously described, with a straight thrust until the slight resistance of the dura is felt to give way, when the obturator is withdrawn and the fluid allowed to flow. There is usually no harm, and often a distinct advantage, in withdrawing all the fluid possible until the normal rate of flow of from four to eight drops per minute is obtained, but the pressure should not be reduced too suddenly. To obviate this the obturator may be inserted in the needle from time to time, or the rubber tube pinched slightly if this has been connected. If the fluid stops flowing suddenly or fails to start, the obturator should be introduced to clear the lumen, and if that fails, the needle should be reintroduced in a slightly different direction or at a different level. If the fluid is at all turbid, save from accidental bleeding, from 20 c.c. to 30 c.c. of antimeningococcus serum should be inserted—a few cubic centimeters less than the amount withdrawn—even though there is a strong suspicion that the meningitis is due to another organism. The spinal fluid obtained should be guarded against contamination, antiseptics, heat over body temperature, and chilling, and should be taken immediately to the laboratory for bacteriological examination.

(c) *Examination of the Spinal Fluid.*—In meningococcus meningitis the fluid is typically under pressure, increased in amount, and turbid with cells which are almost all polynuclear leukocytes. But there are wide ranges from complete macroscopic clarity to pure pus; it is practically always abnormal in amount, or in content, or both. The cellular content may range from about 50 per cu. mm. to hundreds of thousands. A mononucleosis, though unusual, is not inconsistent with meningococcus infection. The one important finding is Gram-negative diplococci, intracellular or extracellular, in smears; these should prove on culture to be meningococci.

Absence of organisms in a turbid fluid is held to be strong evidence of meningococcus infection, because in meningitis due to other pyogenic organisms, such as the pneumococcus, streptococcus or staphylococcus, the cocci are usually readily demonstrable in the first smear. The reverse is rarely true, and the tubercle bacillus, which is notoriously difficult to find in meningeal smears, may cause a slight turbidity.

Bloody fluid probably means that a vessel has been punctured by the needle, but if the blood is evenly distributed it may be due to a hemorrhagic exudate. A yellow fluid coagulating spontaneously (syndrome of Froin) is due to an old hemorrhage.

The chemical tests for albumin and globulin are chiefly of value in differentiating the clear fluid of meningismus from those of poliomyelitis and early meningitis. The albumin and globulin are both increased in cerebrospinal fever.

Fehling's solution in severe cases shows little or no reduction. Prolonged absence of the glucose which is normal in the spinal fluid is an unfavorable sign.

2. *Examination of the Blood.*—The polynuclear leukocytosis of cerebrospinal fever is characteristically high, being over 15,000 in two-thirds of the cases, though cases without leukocytosis are not of great rarity. There seems to be no great prognostic weight to be attached to the white cell count and even in diagnosis practically all meningitides, including many cases of tuberculous meningitis, are likely to show polynuclear leukocytosis.

The presence of the organism of the disease in stained blood films from rapidly fatal cases of cerebrospinal fever has been reported by Andrewes (1906), Coles (1915), Anderson, McNee, Gray, and others (1917), and King (1918). Krumbhaar and Cloud (1918), and Netter and Salanier (1917), found the cocci in smears from the purpuric areas. It may be, as King points out, that search would reveal them in a considerable proportion of septicemic cases, but it is hardly likely, since it is usually necessary to inoculate several c.c. of blood to secure a growth of meningococci.

The frequency of meningococcus septicemia is not settled, but is a question of considerable importance in the pathogenesis and treatment of the disease. Positive blood-cultures were obtained by Gwyn (1899), Salomon (1902), Elser (1905), Jacobitz (1905), Martini and Rohde (1905), Robinson (1906), Marcovich (1906), Andrewes (1906), Davis (1907), Bennecke (1907), Duval (1908), Herford (1908), Liebermeister (1908), Stade (1908), Weiss-Eder (1908), Bovaird (1909), Cecil and Soper (1911), Handa and Nanjo (1913), Mackarell (1915), Bray (1915), Worcester-Drought and Kennedy (1916), Raffaeli (1917), Marie (1917), Pybus (1917), Anderson and others (1917), Thomsen and Wulff (1917). It is noteworthy that the greater portion of these reports are of severe cases. Some of the cases have been of subacute septicemia with meningitis delayed in appearance, or absent altogether. The existence of occasional cases of meningococcus septicemia, or of local meningococcus suppuration, without meningitis, is thus well proven. Recently Herrick (1918, 1, 2, 3) has described from his extensive experience at Camp Jackson a more or less characteristic prodromal stage of meningococcus septicemia before the usual meningitis, and from his laboratory there have been reported two series of consecutive cases showing a high percentage of positive blood-cultures. The first (Baeslack and others, 1918) of 22 cases gave 8, or 36 per cent., positive, of which 50 per cent. died, while 7 per cent. of the cases with negative blood-cultures were fatal. The second series (Herrick, 1918, 3, footnote 2) of 15 cases by Barber and Fleming gave 12, or 80 per cent., positive; the mortality is not stated.

The symptoms described by Herrick for the septicemic stage are malaise, a resenting of interference; frequently coryza, tonsillitis, pharyngitis or laryngitis; apathy, fever, headache, suffused conjunctivæ, petechial rash, asymmetrical deep reflexes, with little or no change in the spinal fluid. Though the uniform existence of such a stage has been a favorite hypothesis of many of the best workers in meningitis, this is the first evidence on a considerable scale in this direction which correlates the clinical with the laboratory findings. Unfortunately the time of appearance of these findings with reference to the positive blood-cultures and to the positive or negative results from lumbar puncture in the series of cases are not given. In an epidemic almost as intense at Camp Beauregard, Maxey (1918), using a technic similar to Baeslack's, found only one case with positive blood-culture preceding the positive spinal culture out of 27 clinically suggestive patients. It may well be that with improved technic the septicemic stage can be proven for the ordinary non-fulminating case. Elser and Huntoon (1909), using the same ascitic broth dilution method (transplanting to ascitic agar plates) which they found reliable for cerebrospinal fluid, succeeded in obtaining positive blood-cultures in 27 per cent. of 41 cases; but they conclude that these were instances of a transient invasion of the bloodstream, rather than an actual proliferating septicemia demonstrating a hematogenic origin of the disease. The method of Baeslack was somewhat similar. Thomsen and Wolff shook the broth into foam before planting, so as to promote a superficial aërobie growth from the blood. The method used by Barber and Fleming is not given.

3. *Nasopharyngeal Cultures*.—The cultivation of the meningococcus from the nasopharynx, as is done in the search for carriers, was formerly used to some extent for diagnosis where lumbar puncture was refused. But now that the necessity for prompt lumbar puncture and treatment has been shown, as well as the fallibility of diagnosis from nasopharyngeal cultures—since a considerable proportion of the population harbors the meningococcus in the nasopharynx—lumbar puncture or blood-culture should be the only reliance for diagnosis. In case these are negative at the time, the accessory information of a nasopharyngeal culture is of some value. Not all cases of the disease yield a continuously positive nasopharyngeal culture.

Diagnosis.—The one keystone in the DIFFERENTIAL DIAGNOSIS of cerebrospinal fever is the bacteriological examination of the spinal fluid. *Tubercular meningitis* is normally the commonest form of meningitis and may closely simulate meningococcus meningitis, though the onset is likely to be more gradual, the spinal fluid practically clear, with, as a rule, more mononuclear than polynuclear cells; in about 90 per cent. of the cases, tubercle bacilli may be found in the fluid if the search in smears from the fibrin web or from the sediment is careful and prolonged. Results from the inoculation of guinea pigs with the sediment are too slow to be of much service. Pulse irregularities, stupor instead of irritable delirium, and indications of cerebral tract involve-

ment such as Babinski's sign, are more common in tubercular meningitis, but none of these criteria are absolute. (See p. 107.)

The other primary purulent meningitides are only differentiated from meningococcus meningitis by the presence of the organisms concerned, in the turbid spinal fluid. A meningitis occurring in the course of another infection such as a pneumococcus pneumonia or a streptococcus otitis may be due to the meningococcus. Though practically always fatal in a few days, cases of recovery are on record after meningeal infections with the pneumococcus, the streptococcus and the influenza bacillus, as well as with the tubercle bacillus. Not infrequently pneumococcus meningitis shows few of the typical meningeal signs. This may be for two reasons: on account of its predilection for the very young, and because the convexity of the brain may be the only area attacked. Unless there is such a localization, the pyogenic organisms are readily demonstrated in smear preparations from the sediment. A purulent fluid without bacteria usually means meningococcus meningitis, a clear one, under pressure, tuberculous meningitis, poliomyelitis, meningismus or cerebrospinal fever in an early or inactive stage. In many septiciemias the organisms are found in the cerebrospinal fluid; a series of five cases of anthrax meningitis has lately been reported by Reece (1917). A relatively benign meningitis may accompany mumps.

Poliomyelitis may occur with sufficient meningeal disturbance to simulate closely cerebrospinal fever, but the typical case of poliomyelitis has only a slight degree of clinical meningitis: the children are able to lie on their backs, and there is more stiffness of the lower spine than of the neck. During an outbreak of poliomyelitis there are doubtless many cases of cerebrospinal fever which fail of spinal puncture and proper treatment because they are mistaken for the prevailing disease. The normal prevalence of poliomyelitis in non-epidemic times is about 10 paralytic cases per 100,000 per annum (Leake, Bolten and Smith, 1917, p. 1999; Lavinder, Freeman and Frost, 1918, pp. 66, 86, 87, 97). The spinal fluid of poliomyelitis is typically clear, under pressure, containing glucose and an excess of albumin and globulin, with a cell-count of over 10 per cu. mm. The high cell-count occurs earlier than the increase in globulin and albumin.

The most frequent and most puzzling condition which presents itself for differential diagnosis is the *meningismus* of other febrile infectious diseases. In children particularly, an acute infection with toxemia is likely to produce meningeal symptoms, usually associated with an increase in the amount of cerebrospinal fluid, but almost always without deviation from the normal in its chemical or microscopic characteristics. Pneumonia, scarlet fever, measles, typhoid fever, malaria, also spirochetosis or infectious jaundice, as reported by the French, may thus be mistaken for meningitis. The only safe rule with these, as with the other diseases, is that lumbar puncture and a study of the spinal fluid be made whenever the meningeal symptoms are definite, both for the sake of diagnosis and to relieve the intracranial pressure.

Sunstroke, tetanus, intoxications, influenza, rheumatism, typhus

fever, meningeal hemorrhage and renal disease may simulate cerebrospinal fever and require puncture. In children digestive disorders, tetany and spasmophilia can usually be differentiated by a thorough history and physical examination.

Complications and Sequelæ.—The complications of cerebrospinal fever may be due directly to the meningococcus or to other causative agents. Among those of the former class, *internal hydrocephalus* has previously been mentioned. It is caused either by a closure of the median foramen of Magendie and the lateral foramina of Luschka (Key and Retzius) in the roof of the fourth ventricle, preventing the ventricular fluid from reaching the subarachnoid space where it can be absorbed, or by the shutting off and damaging of so much of the subarachnoid space by exudate and adhesions that absorption is hindered. In either case the fluid secreted by the choroid plexus in the ventricles of the brain is under high pressure, producing a bulging fontanel, or a positive MacEwen's sign if the fontanels are closed. It is worthy of note that hydrocephalus may occur with the foramina of the fourth ventricle open, so that lumbar puncture actually yields fluid in abundance, though the absorbing surface of the cerebral arachnoidea is cut off by adhesions encircling the base of the brain (Dandy and Blackfan, 1917). In the presence of actual inflammation, hydrocephalus is practically always accompanied by increased retraction of the head and by Kernig's sign, which may be absent in the chronic hydrocephalus subsequent to the meningitis. Mental deterioration or sudden death is to be feared in latent hydrocephalic cases.

Relapses of cerebrospinal fever after complete convalescence are very uncommon. No case is on record of a second attack of meningitis due to a type of the meningococcus different from that causing the original attack.

Meningococcus septicemia has been mentioned. Metastatic foci not infrequently occur even in mild forms of the disease. *Arthritis* due to the meningococcus may be single or multiple and is not as serious as to outcome as might be imagined; it must be differentiated from a serum arthritis which may accompany an urticaria about nine days after the injection of serum. In some epidemics meningococcus *conjunctivitis* and meningococcus *epididymitis* are not rare. *Iridocyclitis* seems to have been particularly frequent with the French. Otitis media may or may not be due to the primary infecting organism. Endocarditis with Gram-negative cocci demonstrated in the vegetations has been repeatedly reported, though valvular disease is not to be feared in the recovered cases. Pneumonia may be due to the meningococcus, but more frequently other organisms are found.

Of central nervous disturbances, blindness is more frequent in infants, *deafness* in adults. Localized paralyses occur, and may be permanent, but they are so unusual that unless they are clearly spastic, or unless the meningococcus was demonstrated in the acute illness, the history should be carefully scrutinized to exclude poliomyelitis. Transi-

ent facial palsies are not uncommon. Mental defects and epilepsy are much less common following meningitis than is generally supposed.

Of non-meningococcal complications bed-sores and cystitis are particularly to be guarded against; the usual sordes and foul condition of mouth and throat no doubt favor the development of the frequent infections leading from the upper respiratory tract, and of pneumonia.

The necessary treatment of the disease may bring on some untoward results, the more serious of which are avoidable. A certain percentage of the cases may be expected to have a *serum rash*—usually urticaria—from one to twenty days after the first serum injection, and some joint pain and fever may accompany the rash, as is the case with the antitoxin rashes in diphtheria. Unless the patient is naturally or artificially sensitized, these eruptions usually take more than a week to develop; they are relieved by cooling lotions or by menthol ointment. For more immediate anaphylaxis, epinephrin or atropin applied subcutaneously are valuable. The serum may also cause a meningeal reaction lasting about twelve hours, and characterized by an increase in the symptoms, and perhaps by a more purulent spinal fluid—a so-called aseptic meningitis. If the meningococci have disappeared, simple lumbar puncture is indicated under these circumstances. Coming on in the course of treatment, these symptoms are akin to the skin reactions observed particularly during the second week of the Pasteur treatment for rabies. Too rapid injection of serum, or too great a volume, produces a very severe and sometimes fatal condition of shock or collapse. Of course, the appearance of Gram-positive staphylococci in the spinal fluid means that there has been at some time a break in asepsis and that the patient has thereby contracted a fatal form of meningitis.

But aside from organisms introduced at lumbar puncture, mixed meningeal infections are not very rare. Councilman, Mallory and Wright report one case which might have been due to the tubercle bacillus and to the meningococcus. Netter and Salanier report two, Mathers one, and Fitzgerald three cases of pneumococcus meningitis superimposed on cerebrospinal fever. This is of interest as indicating that when the barriers are broken down for one form of meningeal infection, they are weakened for others, and also as indicating the importance of continuing the bacteriological examination of the spinal fluid obtained at each lumbar puncture.

During convalescence from meningococcus meningitis, stiffness and pain in the back, weakness, and a general hypersensitiveness are frequently slow in clearing up.

Clinical Types.—**MENINGITIS IN EARLY INFANCY.**—The existence of a type of cerebrospinal fever in infants which is difficult to recognize by the ordinary signs has been mentioned under Indications for Spinal Puncture. In their studies on internal hydrocephalus Dandy and Blackfan (1914, 1917) find evidences of meningitis in adhesions throughout the subarachnoid space at the base of the skull, both in cases with a history of meningitis early in life preceding the hydrocephalus, and in cases where the hydrocephalus was said to be congenital and no meninge-

tis was known. They show that the great majority of their cases of hydrocephalus result from meningitis, and justifiably reason that chronic hydrocephalus is to be expected following a meningococcus meningitis only. "That a very mild form of what was probably meningococcus meningitis has been the cause of a number of our cases seems evident from some of the histories, but the illness has been so slight and recovery so prompt that the mother has looked on it as a 'cold,' 'stomach trouble,' or some illness incident to teething, and it is only by careful questioning that the illness is recalled. Yet after these mild symptoms hydrocephalus may result." Lesions exactly similar to those known to have been caused by a meningitis were found in cases with proven congenital hydrocephalus. This opens the question of intra-uterine meningococcal infection and hemie pathogenesis. Cases of meningococcus meningitis with bacteriological verification have occurred within the first few days of life. Doubtless others have died without diagnosis. If any benefit is to be given the new-born cases of meningitis, diagnosis and treatment should be prompt. An otherwise unexplainable sickness, with fever, restlessness and twitching, deserves puncture without waiting for definite meningeal signs. Slight degrees of bulging of the fontanel when the infant is not struggling or crying is important and direct evidence of inflammatory tension. The onset may have been gradual and the neck stiffness, Kernig's sign, or a taut fontanel may not appear until irreparable damage has been done. With the foramina in the roof of the fourth ventricle closed by adhesions (obstructive type), or the absorbing surface of the cranial arachnoid similarly shut off (communicating type), hydrocephalus is bound to occur.

POSTERIOR BASIC MENINGITIS.—It is unfortunate that this has commonly been regarded as a distinct form of meningitis instead of as a sequel of meningococcal infection in the very young. In children below the age of two years, as in early infancy, the onset of cerebrospinal fever is often not definitely meningeal. Cases are likely to go without diagnosis longer than in older children. The purulent meningeal inflammation, not intense enough to cause a rapidly fatal issue, becomes localized particularly at the base of the skull. Even though healing takes place to some extent, the exudate and adhesions either close the foramina of Magendie and Luschka, or encircle the foramen magnum so as to prevent free circulation of the cerebrospinal fluid. Both the inflammatory reaction and the increased tension caused by the lack of outlet for the secretion of the choroid plexuses produce the reflex retraction of the head which is so pronounced a feature. Emaciation becomes extreme and the spastic bowing backward of the trunk with hyperextended extremities, infolded phalanges, and upturned eyes forms a distressing and all but hopeless picture. The course of the disease, almost always fatal in this stage, averages six to eight weeks, while the average duration of tubercular meningitis is two and a half weeks; as a rule, cerebrospinal fever is the only meningitis of bacterial origin which is not fairly rapidly fatal.

MILD CASES.—Though the mild cases may begin very acutely, the

somewhat more gradual onset is more frequent in this than in other non-infantile forms. These are the cases which would recover without lumbar puncture or specific treatment, and which distinguished cerebrospinal fever formerly as "That meningitis from which recovery may occur." In general, the onset is similar to that of the ordinary acute case, but after the stage of invasion, improvement definitely sets in and continues.

Whether truly "abortive" cases occur in any number, in the same sense in which we describe "abortive" cases of poliomyelitis—that is, mild cases without the specific localization—is a moot question. Some eminent European epidemiologists (Hirsch, 1866, 1886; Bruce Low, 1916) give credence to reports of large numbers of ambulant, abortive cases. All admit that the type of the disease may vary considerably in different outbreaks. Except possibly in the recent experience at Camp Jackson, the greater number of proven generalized cases with positive blood culture but negative spinal fluid have been severe cases. Occasional mild cases have been reported of definite localization outside of the meninges. It is very possible that failure to demonstrate such mild general infection in the past has been due to the fallibility of our blood-cultural methods, with such a delicately growing organism as the meningococcus. Another explanation may be that the Camp Jackson epidemic was somewhat unusual in its proportion of definitely septicemic cases. Despite investigations made to that end, it usually happens that no more cases of indefinite illness, meningism, or "influenza" are observed among those who are isolated as carriers of the meningococcus than would be expected in an indiscriminate group. Analogy with other diseases gives every reason for the belief that such abortive cases of cerebrospinal fever occur; but that their number is generally large is still undemonstrated. For practical purposes, a case of cerebrospinal fever should be expected at some stage of the disease to show definite signs of meningitis, such as a degree of neck rigidity, Brudzinski's or Kernig's sign. During epidemic times, it may frequently be wise to administer serum intravenously and intraspinally before these signs appear.

ORDINARY ACUTE CASES.—After the usual acute onset and twenty-four hours or more of increasing symptoms there is not infrequently a stationary period or slight remission. The signs pointing to the meninges may not be clear for one or more days. Even if the primary lumbar puncture is unfortunately delayed beyond the first day, a relatively clear fluid may occasionally be obtained, though in the thirty cubic centimeter bottle some slight cloudiness can usually be detected in the earliest punctures. Under proper active treatment these cases may be expected to improve, though not without relapses, so that the spinal fluid is free from meningococci in one to three weeks, and the symptoms gradually subside. Kernig's sign and some neck stiffness are among the last symptoms to disappear. If the case is progressing favorably, glucose should appear in the spinal fluid after a few days of treatment, so that Fehling's solution is reduced to a degree approximating that in normal fluids.

In spite of treatment some cases of this group will persist to a chronic stage, and some will go on to an acutely fatal termination within a week.

SUBACUTE AND CHRONIC TYPES.—The more protracted stages may be divided into those in which the persisting infection is the overshadowing picture, and those in which hydrocephalus is predominant. Meningococcal meningitis is by nature relatively mild, since it is the only bacterial infection of the meninges, recovery from which occurs spontaneously in any considerable number of cases. There are cases, therefore, in which the bodily defenses, with or without specific therapy, are nearly able to overcome the infection, but in which the organisms, protected from entire elimination, are able to prolong and renew the fight until the exhaustion of one side or the other determines the issue. If serum treatment is used this may occur either because the variety of meningococci is resistant to the particular serum employed, the pus sometimes becoming too thick to flow through the needle, or because the pus is localized in pockets which are not adequately drained, and which the serum does not reach. In such cases the symptoms of the acute stage are prolonged, often with remissions of greater or less degree; irregular febrile exacerbations with emaciation, stiffness of the neck, Kernig's sign, and a semi-delirious stupor are prominent in these stages. In the less purulent hydrocephalic cases, the fluid obtained at successive lumbar punctures gradually clears, then becomes decidedly lessened in amount, till practically dry taps occur. Coincidentally the symptoms are aggravated, particularly headache and opisthotonos. The condition is akin to the posterior basic meningitis of the very young.

HYPERACUTE AND FULMINATING CASES.—These cases are even more characteristic of epidemics of cerebrospinal fever than are the posterior basic cases characteristic of the sporadic appearance of the disease. The occurrence of even one of these rapidly fatal cases should be enough warning to put an entire community in readiness for an outbreak by securing ample supplies of serum and providing every facility for rapid diagnosis and treatment. The most intense cases may be fatal within four to twenty-four hours of the first known symptoms; sometimes they are overwhelmed by the infection before clearly localizing symptoms have appeared. The patient retires after a day of customary activity and is found in a coma in the morning, or falls down in the street. Perhaps a hemorrhagic eruption, appearing before death, gives a clue to the true disease, though external evidence of meningitis is lacking. The symptoms are those of collapse. In other cases malaise, headache, vomiting or a chill may precede the unconsciousness by a few hours, and some stiffness of the neck or a Kernig's sign be found before death, which occurs from one to three days later. Purpuric eruptions are especially frequent in the very severe cases, though different epidemics vary widely in this respect, as well as in the relative number of such hyperacute cases. It is particularly in the earlier part of a local epidemic that one expects the most foudroyant cases, and the number of deaths within twenty-four hours of the onset is always small.

As has been mentioned, the fulminating purpuric cases are more likely to yield positive blood cultures than are the ordinary type, yet even here spinal puncture is usually positive. If the spinal fluid and the medium are kept at body temperature, and if the medium is properly prepared and is used while moist, meningococcus colonies appear; the diplococcus can also usually be demonstrated in stained smears from the centrifuged sediment. It is astonishing how early in the disease the cerebrospinal fluid may be frankly purulent.

Treatment.—**PROPHYLAXIS.**—*General Protective Measures.*—Bed-side prophylaxis is important in all cases, whether an epidemic is present or not, on account of the possible, though remote, danger from the individual case. Intimate contact with the sick and with his associates should be avoided as far as possible; one, at least, of the latter is a carrier. In a hospital ward, where other diseases are being treated, the beds should be spaced at least eight feet apart and adequate ventilation maintained. In cramped quarters much can be accomplished by “staggering” the beds, so that the foot of one bed intervenes between the heads of two others.

Meningitis is in general no more contagious than typhoid fever or pneumonia. Secondary infections in one household are unusual, but for all infectious diseases contracted by way of nose or mouth, **aseptic nursing** should be enjoined. After caring for the patient, the nurse should wash her hands in an antiseptic solution, and all persons should avoid a zone of six feet from the patient when the latter is coughing or phonating. Visits from relatives and friends are unnecessary and may be harmful even in non-epidemic times. The discharges from the patient should be disinfected if not deposited directly into the sewer. In general, the meningococcus can be counted upon as a quickly dying organism, the danger lying in apparently well carriers, and not in inanimate objects or prostrated patients. **Hexamethylenamin** (urotropin) in 5 to 15-grain doses (0.3 to 1.0 grams) may be given to prevent an infectious cystitis, and also to destroy the meningococci excreted in the urine. It probably has no effect on the meningeal infection (Burnam, 1912).

Notification.—The local health office should be notified by telephone immediately upon suspicion of meningitis, in order that the public may have an early preparation for a possible epidemic, and in order that any laboratory or diagnostic facilities may be placed at the disposal of the physician and patient within twelve hours. Prompt notification of each case to the health authorities enables general measures to be taken at the time when needed. In the presence of an epidemic, these general measures should be carried out, their extent varying with the apparent danger, and with the necessities in each instance. Unnecessary contact among the public at large is to be discouraged—the means of least necessary and of most promiscuous contact being barred first.

General nasopharyngeal cultures were undertaken in the British Army, and a carrier rate of 20 per cent. was considered dangerous, necessitating the **spacing out of the men**, and other measures to reduce

contact. The culturing of all those in more or less contact with actual cases was undertaken in the British and also in the American Army and Navy. In the British Army in England those men were isolated who were found to be carriers of one of Gordon's four epidemic types of meningococcus. In the English Navy at Portsmouth (Fildes, 1918) all new entries were swabbed, all close contacts (about six men to each case) were swabbed twice, and all other messmates of each case of cerebrospinal fever had one culture taken. If any of these were positive, four negative cultures at weekly intervals were required before release. This necessitated three isolation camps, one containing those men on whom report had not been made, a second for those found to be carriers at the last examination, and a third for those found negative at the last examination, pending the fourth negative culture for release. Under such a system it was evident that the number to be isolated would depend upon the number cultured, irrespective of any connection with cases of the disease, and also upon the time and pains spent on the individual cultures and upon the number of negative cultures required for release, since men giving one, two or three negative cultures were not uncommonly found positive at the next trial. The number of colonies to be picked from a plate has also a bearing on the number of carriers found (Vines, 1918). The handling of such a campaign requires not only very competent bacteriologists with good facilities, but also an organization for the isolation of five per cent. or more of those swabbed. Leishman (1918), Mink (1918) and Short (1918) seriously question the advisability of such a procedure. On the other hand, in American camps where the carrier campaign was inaugurated promptly, the meningitis rate appeared to fall more quickly than in the others (Russell, 1918). Even the scientific opponents of Gordon's classification admit that his procedure diminished the spread of the disease (Walker, 1918). In a civil community the search for carriers and their quarantine involves either the missing of such a large proportion of the carriers, or the isolation of so many healthy individuals, as to be impracticable. Attention should rather be directed toward diminishing opportunities for close contact among the population as a whole during an epidemic. There is no means, such as the virulence test in diphtheria, for determining which of the carriers are dangerous.

Individual Prophylaxis.—One definite cause of increased susceptibility may be removed by the **avoidance** of undue exposure to **cold** and to **fatigue**. Various sprays, douches and inhalations have been used to rid the nasopharynx of meningococci and to prevent infection. As ordinarily applied, these can have little if any effect. The localization of meningococci in the folds and recesses of the mucous membrane would necessitate such vigorous application or such strong concentration that the general use of these methods would be out of the question. Cleansing of the throat by **bland washes** is to be recommended.

The wearing of **masks** by attendants on the sick during epidemics has experimental evidence in its favor, as regards the transfer of bacteria. Such masks should be at least six to eight ply and should be

shaped or marked so that the same side is always worn next the face.

Indiscriminate **vaccination**, with suspensions of killed meningococci, has been urged, but there is no proof that meningococcus vaccine has any protective value against natural infection in man; the analogy with typhoid fever and the possibility of the demonstration of antibodies in the blood of the vaccinated have been considered grounds for the practice. On the other hand, we know that meningitis will develop in spite of such vaccination, and since a vaccine powerful enough to develop efficient immunity may do more harm than good, it would appear wise to concentrate effort on the known valuable field of providing prompt diagnosis and proper treatment of the cases as they occur, until it be shown that vaccination is efficient.

GENERAL MANAGEMENT.—The patient's bed should be placed in a room as quiet and as well isolated from the rest of the house as possible. There is probably no acute non-surgical infection, save laryngeal diphtheria, in which **hospitalization** is of as great advantage to the patient as in cerebrospinal fever. For purposes of quarantine, as well as for instant expert medical and nursing attention, and for ready laboratory facilities, a hospital, if properly equipped and available, is to be advised. This is in spite of the fact that most acute infections conveyed through the respiratory tract do better at home than in hospitals. Fluids should be pushed, some liquid being given at hourly or half-hourly intervals when awake. Mouth and throat asepsis requires constant attention, as in typhoid fever.

Diet.—When the vomiting has subsided, the **diet** should be made very liberal. Though the fever interferes with the digestion of any but the simpler foods, these should be made as varied and as palatable as possible, in order to maintain the nutrition. Forced feeding may be necessary when a tendency to chronicity develops.

SYMPTOMATIC TREATMENT.—The primary symptomatic indication is the relief of pain and sleeplessness. Though **bromids**, **hypnotics** or other analgesics should first be tried, the severe headache of cerebrospinal fever usually requires **morphin** unless relieved by lumbar puncture. The meningeal serum reaction often intensifies the headache for a few hours. Since the disease is by no means devoid of the danger of a terminal pneumonia, the depressant should not be pushed or used as a routine, but each dose given according to the indications, in order to gain some sleep for the patient during the twenty-four hours. **Sodium bromid** 1.0 gram (15.5 grains) t.i.d. may partially relax the muscular hypertonicity and act as an adjuvant to the opiate whenever the latter is necessary. **Catheterization** may be necessary for a short period, but the urinary output should be watched from the first, and other means of relaxing the bladder sphincter used if possible. **Cathartics** or **enemata** are usually required for the bowels. *Cardiac stimulants* are rarely advisable. Some English Army officers have used **epinephrin** intravenously or intramuscularly in pulseless fulminating cases with apparent success, giving it in 0.6 to 1.2 c.c. (10 to 20 minims) doses every four hours according to the pulse (MacLagan and Cooke, 1917). It

would obviously be dangerous in the slightly later stage of increased cerebral tension and heightened blood-pressure.

SERUM TREATMENT.—The method of **lumbar puncture** has been described (p. 98). This in itself is distinctly helpful, relieving the cerebral pressure, withdrawing purulent fluid and, possibly, permitting the formation of more antibacterial exudate, though there is no experimental evidence for this last. However, its former chief advocates have been ready to admit that the results with lumbar puncture alone were poorer than those obtained by the combined use of *drainage* and a potent *anti-meningococcic serum* (Dunn, 1911; Netter, 1911; Foster, 1918). But the serum must be introduced at the site of the chief infection, that is, intraspinally, in the subarachnoid space. This necessarily limits the amount that can be given at one time, and prevents the early, intensive application of the antiserum at one dose, as is most successful in diphtheria.

As mentioned previously, lumbar puncture should be performed on suspicion of meningitis, and **antimeningococcic serum** injected at once if the fluid is at all cloudy, without waiting for bacteriological examination. This should be done even with a clear or blood-tinged fluid, if the history is suggestive, and if other cases are occurring. The amount to be injected should be less than that removed. It is safer to give another injection after from eight to twelve hours than to increase the intraspinal pressure by giving a greater amount at the first injection, causing thereby not only pressure symptoms, but a heightened toxic action of the necessary preservative in the serum.

The routine dose is from 20 to 30 c.c. It is safe to go above the latter amount when a very large amount of serum has been withdrawn, and when prior injections in the same patient have been borne without depressant reaction. The injections should be made very slowly, by gravity, the serum having previously been warmed to a few degrees above body temperature. Sophian advises the use of a sphygmomanometer during injection, and the stopping of the serum if the total fall in blood-pressure reaches 20 mm. Due probably to the elasticity of the tissues in children, they can be given practically as large doses as adults, and even in infants the doses are much greater than in proportion to the body weight. Some discomfort is often noted toward the end of the injection, and this, if very severe, is a signal for stopping. Since the amount which can safely be injected is limited, however, every effort should be made to allow this to be maximal, by withdrawing as much fluid as possible previously, and by proceeding with the injection gently and carefully. At the conclusion of each injection, the foot of the bed may be raised six to eighteen inches for three hours, to allow the serum, which is of higher specific gravity than spinal fluid, to gravitate toward the cerebral meninges; for three hours before puncture the head may similarly be raised to facilitate the denser exudate seeking the subarachnoid interstices of the lumbar region.

*Inject*ions should be repeated daily until no meningococci can be found in the spinal fluid, or for four days at least, if they disappear

earlier. If the case is a very mild one, fewer than four will suffice, but even though improvement is marked it is not safe to stop short of overwhelming the infecting cocci as rapidly as possible, in order to prevent the development of "serum-fastness" by the microorganisms, and relapses. Frequently, more than four daily injections are needed, but if symptoms have ameliorated by that time, and if the spinal fluid has cleared to a considerable extent, an interval of forty-eight hours may be permitted to elapse. The serum itself provokes a meningeal reaction which may be severe at times, with headache, pain and more marked retraction for eight hours or more, and this may be reflected by increased cloudiness in the spinal fluid. In order to differentiate this from an infection with a few organisms not growing in cultures, or not seen in smears of the sediment, it is well not only to omit injection for a day or two after the first intensive series, but to perform **lumbar puncture without serum** as a routine toward the end of the treatment. As long as meningococci are readily demonstrable in the spinal fluid, intensive serum treatment is indicated; and if the infection does not yield to eight or ten injections of one serum, another should be tried, preferably a serum which has been matched against the strain of meningococcus obtained from the particular case in question.

If the first intensive series of daily injections has been completed, and meningococci are again found in the spinal fluid, another series of at least four daily injections should be given. The total number of injections necessary may exceed fifteen or twenty.

In very severe cases, valuable time may be saved by giving more than one injection in twenty-four hours, but this advantage is to be weighed against the disadvantage of continuing the possible meningeal reaction from the serum. Josephine Neal, in her large experience with sporadic meningitis in New York City, advises against the more frequent injections. During a highly fatal epidemic and with an alert meningitis hospital service, the eight- or twelve-hour injections are indicated at times.

In case there is prior evidence of severe meningeal infection, and the symptoms persist or increase, but no fluid is obtainable on repeated lumbar puncture, the situation is indeed desperate. One "dry tap" should not prevent repeated trials; bits of exudate or tissue may plug the needle, or the pus may be too thick to flow. Larger and sharper needles should be tried at different levels. The lateral as well as the median route should be used. If under these conditions little or no fluid is obtained, one very possible inference is that the lumbar region is occluded from the secreting ventricular plexuses—most frequently by beginning adhesions in the region of the fourth ventricle, or lower in the vertebral canal. To break these up, Herrick advocates Cobb's device of forcible manipulation of the neck under inhalation anesthesia; this may be followed by a free flow. It is not safe to sit the patient up, and fatal accidents have even followed forced coughing in order to start the flow. Surgical procedures for these obstructions are mentioned below.

In Great Britain and on the continent **lavage** of the spinal space has been performed with saline or with an antiseptic solution. This is *more dangerous than beneficial*. Flexner and Amoss (1916) have shown that many antiseptics actually retard recovery by inhibiting phagocytosis in the spinal fluid.

Fresh normal or convalescent human serum was tested experimentally and injected intraspinally in human cases with varying success by Davis (1907) and by Mackenzie and Martin (1908); it was added to ordinary antimeningococcal serum as complement by Fairley (1916) in Australia, and by Kolmer (1918) in Philadelphia. Although this procedure is theoretically sound, its use was abandoned in Australia, probably both on account of its cumbersome technique and the danger of non-sterility, and because the plain antimeningococcal horse serum used intensively, well controlled bacteriologically, with a lumbar puncture squad watching the patient practically every hour of the twenty-four, gave even more satisfactory results. (*See p. 117.*)

The **intravenous** use of antimeningococcal serum has been practiced from time to time (Nowland, 1916; Stewart, 1917), on the ground of the systemic nature of the meningococcal infection, and it has recently been strongly urged by Herrick and his coworkers. Too little attention has doubtless been paid to this in the past, but it cannot be denied that most cases of cerebrospinal fever, as they come to the attention of the physician, are overwhelmingly meningeal; it is in the meninges that the battle must be fought and won. In very early and obviously septicemic stages the large doses of from 50 to 120 c.c., advocated by Herrick, should be given intravenously, with the precautions observed in serum injections for pneumonia. Even though only minimal amounts of antibodies reach the cerebrospinal fluid from the blood, the excretion of antibodies from the spinal fluid into the blood stream may possibly be retarded by raising the antibody content of the latter. The serum has also been used with success locally, in joints and in other purulent, meningococcal foci; but the arthritis of cerebrospinal fever tends to recover spontaneously.

SURGICAL INDICATIONS.—The most frequent, grave condition for which **surgical intervention** is suggested is internal hydrocephalus, due to a stoppage of the outflow of ventricular fluid. This is probable when little or no fluid is obtained at the lumbar puncture, in spite of headache, with vomiting irrespective of the taking of food, with increasing blood-pressure, nystagmus, dilated sluggish pupils, a slight or considerable bulging of the fontanel in an infant, or with a developing MacEwen's sign in an adult. Optic neuritis, slower pulse rate, increased head retraction might be expected but are very frequently absent, and wasting, impaired mentality and sphincter trouble come too late to be of great help in diagnosis.

In an infant the signs first mentioned are indications for **puncture of the fontanel**. Zingher (1919) believes that persistent dry taps, with slight bulging of the fontanel, when the infant is not crying or struggling, are sufficient evidence for cranial puncture. This may be done

with a needle smaller to that used for lumbar puncture, the head should be tilted without abduction, and moisture of soda applied to the site. The infant is held firmly wrapped in a blanket, one assistant maintaining the head in exact position. Any lateral motion of the needle is dangerous. The sterile needle is inserted at an outer angle of the fontanel, not less than 1 cm. from the median line, to avoid the longitudinal sinus, and pointed very slightly forward. If the site chosen is over 2 cm. from the median line, the needle should also be directed inward at an angle of not more than 20° from the perpendicular, if it is only 1 cm. from the median line the direction should be slightly outward. When a depth of from 2 to 5 cm. is reached the obturator is withdrawn to allow the fluid to flow. The needle must be held very gently, to prevent lateral motion. Serum may be administered as by lumbar puncture. At successive punctures alternate ventricles should be drained, and lumbar puncture be performed at a later date, to ascertain the re-establishment of the spinal circulation. Despite the apparent simplicity of this procedure one cannot escape the impression that the successful cases are reported and many unsuccessful ones unrecorded. Certainly in adults ventricular puncture should be performed only when a personnel is available, which is expert in the strict aspects of brain surgery. Puncture through the corpus callosum (following the falx cerebri, or frontal, temporal, or occipital trephining, may be used. Continental surgeons have not hesitated to puncture at the lower cervical vertebrae, and along the roof of the orbit through the sphenoidal foramen (Doyle, 1918), when there seemed to be a stoppage above the lumbar site. Haynes advocates drainage of the cisterna magna.

By persistent lumbar puncture, with serum injection when indicated, some cases of apparent internal hydrocephalus have been cured. On the other hand, it is by early diagnosis and prompt treatment of internal hydrocephalus that good results may be hoped for.

Enucleation may be needed for panophthalmitis, and **paracentesis** for otitis media.

TREATMENT OF COMPLICATIONS AND SEQUELÆ.—In this wasting disease special care must be taken from the first, and as a routine, to **prevent bed sores**. Alcohol and powder on the pressure points and clean smooth sheets are necessary.

The treatment of hydrocephalus has been mentioned.

The itching serum rashes of the later periods of the disease may be relieved by an evaporating lotion such as:

Chlorali hydrati	10 grams (2.5 drams)
Phenol	2 grams (0.5 dram)
Aq. camphoris	125 c.c. (4.25 fluid ounces)
Alcohol	125 c.c. (4.25 fluid ounces)

or by 5 per cent. menthol ointment. The rare cases of collapse immediately after serum treatment should receive **adrenalin intravenously** in 1 c.c. (16 minims) doses.

Joint complications usually take care of themselves, with local appli-

cations, but may require puncture and serum injection. Therapeutic measures directed against gonococcal conjunctivitis are effective against the meningococcal form, but the more serious ocular conditions start as iridocyclitis, or even deeper in the eye, and may advance very rapidly.

CONVALESCENCE. The subsidence of fever and acute signs of inflammation are usually followed by stiffness, persistent Kernig's sign and by various pains. **Massage** and gentle, **passive exercise** aid in restoration, and do no harm. Restoration to full vigor and activity is frequently very slow, and the patient should be guarded against undue exposure or strain. A degree of internal hydrocephalus may persist, and cause a rapidly fatal issue, without persistent infection, but with the clinical symptoms of relapse.

Prognosis. As to **Recovery.** Just as various outbreaks of the disease differ widely in their symptomatology, some being for example largely eruptive and purpuric, while the nervous symptoms predominate in others, so the case mortality rate varies greatly. The Silesian epidemic of 1905, before serum treatment began, had a mortality of 58 per cent. among 3,102 cases (Westenhofner, 1906). The small 1917 Copenhagen outbreak (Thomsen and Wulff, 1917) had practically 100 per cent. mortality. Sporadic cases in general have a lower fatality than epidemic cases, and the later cases are usually milder than those occurring during the first part of an epidemic. The best body of statistics of serum-treated cases is that of 1,294 collected by Flexner in 1913, showing 18.1 per cent. mortality among those in which the treatment was instituted during the first three days, 27.2 per cent. for those in which it was begun on from the fourth to the seventh day, and 36.5 per cent. for those in which serum was first given after the seventh day; only a small number who died less than twenty-four hours after the injection have been excluded. Some small series have given a mortality rate below 10 per cent.

The most encouraging point in favor of the serum treatment is the evidence that the mortality decreases in proportion as the patients are treated earlier in the attack; all statistics agree on this. The figures are not comparable to those of diphtheria as best treated, but cerebro-spinal fever without serum is a more fatal disease than diphtheria without antitoxin. The difficulties in the way of proper treatment, by reason of the need of continual injections, are also much greater. As the medical profession becomes more adept and more persistent in the treatment, we may expect the mortality to fall. Promptness, persistence and proper technique are nearly as important as the proper serum, but in two instances, in Australia, non-specific horse serum was used on a series of cases, from lack of antimeningococcic serum, with disappointing results (Sandison, 1916).

As an indication of what may be expected with good treatment of

sporadic cases, usually outside of hospitals and in congested parts of the city, the following tables from Neal may be quoted:

MORTALITY IN CEREBROSPINAL FEVER: By years

	Total Number of Cases	Patients Recovered	Patients Died	Results Unknown	Mortality Per cent.
1910-1911.....	17	10	7	0	41
1911-1912.....	24	7	14	3	66
1912-1913.....	30	17	12	1	41
1913-1914.....	41	28	13	0	31.7
1914-1915.....	38	25	13	0	34
1915-1916.....	57	40	17	0	29.8
1916-1917.....	85	65	20	0	23.5
1917-1918.....	112	90	22	0	19
1918-1919.....	78	62	16	0	20.5
1919-1920.....	36	18	18	0	50
1920.....	19	18	1	0	5.3
Totals.....	537	380	153	4	28.5

MORTALITY IN CEREBROSPINAL FEVER: According to age

Age	Cases	Mortality Per cent.
Under 1 year.....	102	46
1 to 2 years.....	46	31
2 to 5 years.....	89	16.8
5 to 10 years.....	108	25.9
10 to 20 years.....	84	23.8
Over 20 years.....	80	31

MORTALITY IN CEREBROSPINAL FEVER

According to time of beginning treatment

Time after Onset	Cases	Mortality Per cent.
1 to 3 days.....	200	23.5
4 to 7 days.....	137	27.7
7 to 14 days.....	63	37
2 to 3 weeks.....	47	47.8
Over 3 weeks.....	22	40.8

It is to be expected that in epidemic periods the mortality in cases seen within the first three days would be reduced below that indicated above for sporadic cases, because in non-epidemic times cases which are not of the very severe type are likely to be misdiagnosed at first and the treatment thereby delayed.

MODE OF DEATH.—The early deaths commonly occur from cardio-vascular failure, with very low blood pressure. Respiratory failure is the usual cause of death, if the first shock of attack has been survived. The cerebral congestion and the internal hydrocephalus both raise the blood pressure, and the respiratory center bears the brunt of the attack, as is evidenced by the irregular respirations. A blood pressure consistently below 120 mm. in the first 60 hours, or above 120 mm. thereafter, is of serious prognostic import. In the chronic stage, death may come from pneumonia (as also in the acute stages), or from malnutrition and exhaustion. (*See p. 96.*)

AS TO DURATION.—Cerebrospinal fever is probably the most generally variable of any infectious disease as to duration. The symptoms in fatal cases may have an observed length of four hours, or of months. Hardly any other diseases met with in this country will kill as suddenly, and with as little evidence of localization, as do cerebrospinal fever and acute poliomyelitis. Flatten (1906) recorded 7.5 per cent. of fatal non-serum-treated cases as dying in the first twenty-four hours, the same number in the second, 24 per cent. in the first three days, 24 per cent. from the fourth to the seventh day, 52 per cent. later than the seventh day, and 7 per cent. after eight weeks or more. Serum-treated cases usually either die early or survive; sudden cessation of symptoms is frequent. This indicates that the problem is to get the serum into the spinal tissues promptly and adequately. So much depends upon the thoroughness of administration of the serum, and upon promptness of diagnosis, that figures as to the length of the convalescence are of little value. (*See pp. 107 and 108.*)

AS TO FUNCTION.—With serum treatment the paralyses and mental deteriorations, which were formerly supposed to follow meningitis in a large proportion of cases, are very few. It is not improbable that many of the paralyses assigned to meningitis were due rather to poliomyelitis. Deafness unfortunately occurs early, often before treatment is instituted, and is still frequent; prompt diagnosis and treatment is our only hope of reducing the incidence of this permanent disability.

Pathological Anatomy.—The earliest anatomical change is a hyperemia of the pia and arachnoid over the brain and spinal cord. Some clouding and edema of these tissues next appear, and faint yellow patches may be visible in places. Microscopically this is seen to correspond to an infiltration with polynuclear leukocytes. Frank pus may then be found, which in the chronic stages becomes fibropurulent, and organizes

into adhesions and thickened meninges. The exudation is most prominent along sulci and around vessels; the base of the brain and the posterior surface of the cord are the chief sites of deposits, but the purulent infiltration usually extends up around the lateral surfaces of the cerebrum, sparing in general the longitudinal fissure, and is abundant over the upper surface of the cerebellum. Collections of pus are found at the roots of the cranial and spinal nerves.

The spinal fluid coincident with these changes is at first nearly clear, then cloudy, and may become actual pus. The cells of the exudate are largely pus cells, but lymphoid and plasma cells may be found in the tissues toward the periphery of infiltrates, and very large cytophagocytic cells are also found. These latter have been described by Councilman, Mallory and Wright as originating from connective tissue cells or from cells lining the lymph spaces. The proliferative endarteritis common in tubercular and pneumococcus meningitis is unusual in this disease.

The ventricles of the brain take part in the process, the subependymal and choroid vessels are injected and the ependyma raised or displaced by edema. The ventricular fluid is cloudy, but does not uniformly correspond with the spinal fluid. Particularly if the collections of pus or adhesions have impaired the free passage of fluid through the foramina of Magendie and Luschka (obstructive hydrocephalus), or if the cerebral meninges have been blocked off by adhesions surrounding the foramen magnum (communicating hydrocephalus), the ventricles are dilated.

The meningeal inflammation frequently extends down into the cortex of the brain, less often into the spinal cord; and cellular infiltrations, not always apparently limited to the periphery of vessels, are found here. Hemorrhages into the nerve tissue also occur, and areas of softening may coincide with paralyses. The cranial and spinal nerve-roots show inflammation and infiltration, and extension of the process along the eighth nerve or along the optic nerve may give labyrinthine deafness or a purulent panophthalmia. Meningococci are found intracellularly and extracellularly in the exudate, more especially in the acute rather than in the chronic stages. The meningococcus also gives rise to a bronchopneumonia, dense enough at times to resemble lobar pneumonia clinically and macroscopically. In such cases meningococci are found in enormous numbers in the pus cells of the pulmonary exudate. Croupous pneumonia as a complication of cerebrospinal fever is due to the pneumococcus. The spleen is enlarged, but not as regularly as in other infectious diseases.

Historical Summary.—The first record of an epidemic of meningitis is that of Vieusseaux, who described an outbreak in Geneva, Switzerland, in the winter and spring of 1805. Doubtless epidemics had occurred before this, but the accounts are dubious, and sporadic cases could not

be distinguished from other meningitides. In 1806, without having heard of the Swiss outbreak, Danielson and Mann described an epidemic in Medfield, Massachusetts, with five postmortem examinations. From that time we know of hundreds of epidemics throughout the civilized world. The division into epidemic periods made by German writers is more or less artificial, though it is evident that even countries such as the United States, in which epidemics are particularly frequent, have been practically free from serious outbreaks, as far as the records go, for years at a time. In France the greater part of the earlier epidemics were among the troops.

The bacteriological history of meningitis begins with the demonstration of the meningococcus in 1887 by Weichselbaum of Vienna. The importance of this discovery was discounted for a number of years by the confusion of the meningococcus with the pneumococcus and other Gram-positive cocci (Jaeger), until such researches as those of Councilman, Mallory and Wright, which were made during the Boston epidemic of 1897, established the correctness of Weichselbaum's original descriptions. In the Portuguese epidemic of 1901-1903, Bettencourt and França found the organism in every one of 271 cases investigated. In 1901 Albrecht and Ghon first showed the presence of the meningococcus in the nasal secretion. The Silesian epidemic of 1905 comprised 3,317 cases and furnished the material for von Lingelsheim's thorough bacteriological work. This epidemic lingered till the Rhenish-Westphalian outbreak of 1907, and these, together with the New York epidemic of 1904-1905, instigated the preparation and use of the serums of Jochmann, Kolle and Wassermann, and that of Flexner. One of the most extensive recent epidemics, aside from those coincident with the concentration of troops for the war, was that of 1911-1912 in the southwestern United States.

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CHAPTER VII

DIPHTHERIA

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Definition, p. 131—Etiology, p. 131—Predisposing causes, p. 131—Exciting cause: the organism, p. 132—Symptomatology, p. 135—Clinical history, p. 135—Second attacks, p. 137—Diagnosis, p. 137—Differential diagnosis, p. 138—Complications and sequelae, p. 143—Association with other diseases, p. 146—Clinical varieties, p. 148—Treatment, p. 151—Prophylaxis, p. 151—Schick test, p. 154—General management, p. 160—Medicinal treatment, p. 160—Local treatment, p. 161—Surgical treatment, p. 162—Intubation, p. 162—Extubation, p. 162—Tracheotomy, p. 163—Treatment of complications, p. 164—Management of convalescence, p. 165—Prognosis, p. 166—Pathology, p. 166—Historical summary, p. 169.

Definition.—Diphtheria is an acute contagious disease, caused by a specific organism, characterized locally by the presence of a false fibrinous membrane and systematically by cardiac and nervous manifestations, due to the production of a specific toxin. The site of infection is, in the vast majority of cases, the membrane of the throat; sometimes the nose and the larynx are involved, and more rarely the conjunctiva and cutaneous surfaces that are deprived of epithelium.

Etiology.—PREDISPOSING CAUSES.—Diphtheria is distributed practically all over the world and is endemic at all times, although it seems to show a preference for *northern climates* and for the cold, damp, winter months. *Sudden changes in temperature* from warm to cold seem to affect the incidence and the mortality of the disease. This fact is probably due to the catarrhal conditions of the nose and throat which result from a sudden fall in temperature, and which favor the lodgment and the growth of the diphtheria bacillus in these parts.

Diphtheria is decidedly a disease of *childhood*, without any noteworthy distinction as to *sex*. The susceptible period is that between the second and twelfth years, the most critical time being between the second and fifth years. Infants enjoy the same comparative immunity as they do from other acute infections. Adults, though less susceptible than children, may contract the disease at any time, although it is rarely seen in old age.

The general susceptibility to diphtheria is, on the whole, not nearly so marked as is the case with scarlet fever or measles. Observations show that in the vast majority of individuals who have been exposed to the disease, although the diphtheria bacillus is present, the infection never develops. Any personal predisposition that exists seems to be attributable, primarily, to the *condition of the mucous membranes*, particularly those of the nose and throat. Children who have adenoids, large or diseased tonsils and chronic inflammation of the nasopharynx,

or deformities of the nasal septum, are much more likely than others to contract the disease. This is sometimes termed an increased superficial predisposition, and may also result from any other abnormalities of the pharyngeal or nasal regions.

The presence of another acute infection, particularly when of the anginose variety, such as scarlet fever and measles, is an important factor in the etiology of diphtheria. In such instances the throat conditions present a most favorable opportunity for the diphtheria organism to become active.

The disease is in no way dependent upon *social conditions*, the rich and the poor being equally susceptible, except that, as in other infections, bad housing conditions, poor drainage, under-nourishment, etc., increase the disposition of the less-favored classes to disease in general. This applies also to *local racial conditions* and accounts for the apparently greater prevalence of the disease among the colored population in a given locality.

EXCITING CAUSE: THE ORGANISM.—Diphtheria is one of the few diseases the specific organism of which is known, and for which there is a specific treatment. To Klebs belongs the distinction of having first described the diphtheria organism (1883), while Löffler (1884) was the first to obtain it in pure culture. Later (1887), he succeeded in producing the disease in guinea-pigs. It is known to be also transmissible to other animals—cats, dogs, horses and goats. Shortly after Löffler's demonstration, Roux and Yersin (1888) were able to show that the symptoms of diphtheria were due largely to a soluble toxin which is not part of the organism, but is secreted by it. Acting upon this suggestion, Ferran, and later Fraenkel and Brieger (1890), attempted active immunization against diphtheria with the toxin. At the same time von Behring made his discovery of the antitoxin, and after prolonged research in collaboration with Wernicke he was able to demonstrate by animal experiments the prophylactic and therapeutic value of the antitoxin. The first clinical tests on the human subject were made (1891) in von Bergmann's clinic at Heidelberg. The method at once gained adherents and, through the impetus thus acquired, it has become probably the most significant and valuable contribution to preventive and therapeutic medicine.

Morphology.—The Klebs-Löffler bacillus is aerobic, being most satisfactorily cultivated in an alkaline medium (Löffler's blood serum) at a temperature of about 98° F. (36.6° C.). It is generally described as a gram-positive, rod-shaped, slender organism with rounded ends, varying in size from 1 to 6 microns in length and from 0.3 to 0.8 microns in diameter. It is easily stained with aniline dyes, the Löffler alkaline solution of methylene blue being among the best and the one in which it appears smallest and most constant. Its appearance, however, is not altogether constant, polymorphism being one of the characteristics of the diphtheria organism. Westbrook, whose classification is the one generally accepted, divides it into three morphologic groups, each with subdivisions according to the size of the organism. The first group is the beaded or granular type (with deep-staining granules) and is designated A, B, C, D; the second is barred or banded (having transverse bands), and is designated A₁, B₁, C₁, D₁; the third is a solid type taking an even stain, and is known as A₂, B₂, C₂, D₂. Westbrook, in his original group-

ing, recognized variations up to the letter G, but in the average laboratory the above subdivisions have proved sufficient.

Ordinarily, cultures are pronounced positive only when they show: A or A₁, B or B₁, C or D. C₁, D₁, the shorter barred forms, and B₂, C₂ are considered avirulent, but cultures showing these and other atypical forms should not be pronounced negative until they have been reincubated for another 24 hours; unless the field, after the second incubation, shows the above positive types (A or A₁, B or B₁, C or D), the culture can be considered negative.

The granular type is the one most commonly seen early in the disease, whether it be localized in the nose, the pharynx or the larynx. This type is liable to prove virulent even in prolonged culture cases, so that contacts showing it should be held under suspicion of being dangerous until proved otherwise. Later in the disease this type is supposed to be replaced by the barred or by the solid forms. This, however, is a matter of controversy.

The solid type is the most serious form. The bacilli of this group are few in number and are replaced later by the granular type. It is generally supposed to be present only in the late stage of the disease, but some authorities believe that it is also present in the earlier cultures, but is overshadowed by the granular type.

It is when this type predominates that the advantage of animal inoculation is greatest. The longer bacilli show a greater tendency to retain their virulence than the shorter ones. Both, however, may be descendants of the so-called carrier bacillus rather than of the organism that produces the clinical evidence of the disease. The shorter, solid types are most frequently found in the nose when clinical manifestations of diphtheria are absent. In a majority of cases these bacilli are not pathogenic, although in a small percentage they are virulent, as proved by animal inoculation.

The long solid types are frequently found in otitis media, and as a rule they are avirulent.

Cultivation.—Diphtheria bacilli can be cultivated without great difficulty on the ordinary laboratory media. They are usually associated with other organisms in the throat, however, and may be isolated most easily on Löffler's blood serum. On this medium the organisms grow rapidly, appearing in 12 to 15 hours as small, discrete raised colonies, pearl gray, whitish-gray, or yellowish-gray in color. A visible growth sometimes appears in six hours at 37° C. (98.6° F.). By the end of 24 hours the colonies are much larger—smaller than staphylococcus colonies and larger than streptococcus colonies. Older colonies are larger, less glistening, with irregular edges and sometimes concentric rings of growth or fine radial striations. The colonies may remain isolated, or may coalesce to form a moist, thin grayish-white or grayish-yellow expansion which is usually limited to the line of inoculation. Some cultures have a yellowish color on Löffler's serum, others are pale red, and quite old cultures are dark brown or black.

Staining Reactions.—The diphtheria bacillus stains by all the aniline dyes but seems to have a special affinity for alkaline methylene blue (Löffler's). Stained by this dye it shows a peculiar segmentation into granules, which makes it resemble a streptococcus. The granules may be brought out by a double staining with carbolfuchsin and methylene

blue (Escherich's), appearing red in a blue background. Granules staining with methylene blue are present in nearly all true diphtheria bacilli, but also in closely related organisms like the *Bacillus xerosis* (Ernst). They are usually called Babes-Ernst bodies and are no longer regarded as spores. They are more common in bacilli taken from the membrane than from cultures, more common in young cultures on Löffler's serum than on agar, on gelatin, or in broth. Granules may be demonstrated by Neisser's stain (acetic acid methylene blue followed by Bismarck brown) and by those of Roux and Yersin, Löffler, Falieres, and Lubinsky, among others. The diphtheria bacilli are always gram-positive.

Attention is called at this point to the pseudodiphtheria (Hoffmann) bacillus and *Bacillus xerosis*, which often enter into consideration in differential diagnosis and which are frequently seen in the conjunctival fluid. The differentiation is best made by acid production tests, the most satisfactory medium being Hiss' serum-water, colored with azolitmin and containing 1 per cent respectively of the following sugars: glucose, saccharose, dextrin, lactose, maltose, galactose and mannite. The results are recorded after the cultures have been incubated for five days at 95° F. (35° C.); the presence of acid is shown by the blue turning to pink or red. Virulent diphtheria bacilli frequently produce acid with dextrose and dextrin in the order mentioned; the results with the other sugars are variable. Cultures which prove negative as far as the structure of the organism is concerned but produce acids with some of the sugars, notably glucose and dextrin, are to be regarded as nonvirulent diphtheria bacilli, and a negative report should be given when they appear in cultures.

These sugar tests are most useful in studying cultures from the eye, and are the only means of differentiating the short solid type from the Hoffmann bacillus and the *Bacillus xerosis*. If the culture proves nonvirulent for guinea-pigs, and produces no acid with any of the sugars, it is regarded as containing Hoffmann bacilli, while nonvirulent types that produce acid with saccharose are regarded as cultures of *Bacillus xerosis*.

Distribution.—The diphtheria bacillus differs from other pathogenic organisms by the fact that it is widely distributed throughout the body. It is found not only on the surface of the affected mucous membrane, and in the superficial portions of the false membrane and its underlying tissues, but also, in the severe cases, in the heart-blood, the liver, spleen and kidneys.

The most important characteristic of the diphtheria toxin is its ability to stimulate the production of antibodies which, when injected into the human body in proper doses, create a certain degree of immunity and resistance to the disease.

Modes of Conveyance.—The source of contagion of diphtheria is pre-eminently the human subject, that is, the diphtheria patient, who emits infected droplets while talking or coughing. Tracheotomized croup cases are a most dangerous source for the spread of the disease, since such patients are apt to cough up shreds of membrane through the cannula.

There is little positive evidence that the soil, the water or the milk supply are factors in disseminating diphtheria, except that impurities in the water or the milk, or defective drainage may be responsible for the lowered resistance of the mucous surfaces to disease.

The diphtheria bacillus is remarkably resistant to cold, retaining its

virulence for several months during the winter, but its resistance is lowered by exposure to light and to moisture. It shows no particular resistance to disinfectants, but it is apt to retain its virus to a remarkable degree for many months if protected from light, and allowed to dry, for example, on a *particle of membrane*, or on *fomites*, such as toys, books, eating and cooking utensils, or, more especially, on *bed and body linens* that have come in contact with a diphtheria patient. According to some authorities the bacillus is also present in the *urine* of patients, and the nurse or attendant is apt to be infected in this way unless properly protected.

Danger of contagion persists into the period of convalescence and beyond it, even into the ninth week or longer. The observation that the diphtheria bacillus on the membrane of convalescents often retains its virulence for a more or less prolonged period after convalescence, together with the fact that healthy individuals in the vicinity of the diphtheria patient also harbor the specific organism, is supposed to account for certain mysterious epidemics of diphtheria through the medium of such direct and intermediary *carriers* of the organism.

Symptomatology.—CLINICAL HISTORY.—*Period of Incubation.*—The typical symptoms from the bacterial toxin are manifested by local and general phenomena.

For various reasons the incubation period of diphtheria cannot be definitely determined, but it is generally short, from two to four days, rarely exceeding seven days, depending on the virulence and the number of organisms present, and on the susceptibility of the individual. The maximum incubation period has lost its importance since the introduction of the custom of culturing the throats of all contacts as a routine measure.

The diphtheritic membrane is apt to develop in different parts of the body. Its clinical course depends upon the particular location in which it is deposited, the most common situation being the faucial region, which will serve as a basis for description of the clinical history of the disease.

Mode of Onset.—The early symptoms are the languor, apathy and general loss of appetite and vigor that accompany an incipient cold. This may last a day or two before the child complains of *pain in the throat*, although sometimes, aside from the general malaise, sore throat is the only complaint. More rarely the invasion is sudden, accompanied by chills, high fever, 100 to 103° F. (37.8 to 39.4° C.), headache, nausea and vomiting, together with the throat symptoms; but the last sometimes do not appear until the end of the first, or the beginning of the second, day. It is important to remember that the degree of fever is no criterion for the future course of the disease. It may be low at this stage in a severe and fatal case, or high in what proves to be a mild case. At this early stage the patient will present a pallid countenance, rapid soft pulse (110 to 120), and a disagreeable odor from the mouth. The tongue is dry and moderately coated; the faucial mucosa is slightly reddened and shows increased mucous secretion. Sometimes one or even both tonsils will be the site of a small, grayish-opal coating or of a grayish, cloudy patch. The membrane at this stage is only slightly adherent and can be easily and safely removed. It will be found (under the microscope) to consist of fibrin, epithelial cells, leukocytes, diphtheria

bacilli and the usual buccal flora. If removed, the membrane rapidly reforms; when allowed to remain it becomes firm, consistent and more intimately adherent to the underlying tissues, with a tendency to spread to the surrounding structures—the anterior and posterior pillars of the fauces and the lateral margins of the uvula—the latter often being so entirely covered as to suggest a finger encased in a glove.

Within the next 24 hours the membrane assumes its characteristic grayish aspect, the intensity of color depending upon the other organisms present. When thin the membrane is translucent; it may also be a pale yellow or a dirty white or even dark, almost black, if there is bloody effusion. It is now tough, firmly adherent, and when removed leaves a raw, bleeding surface. Later on in the course of the disease, as the membrane begins to separate of its own accord, it can be removed without producing bleeding.

The subjective symptoms produced by the presence of the membrane on the throat are burning and difficulty in swallowing; the swelling of the tonsils makes the voice rough and thick, while the inflammation may, as early as the first day, cause enlargement of the glands, especially the maxillary, those at the angle of the jaws and the anterior cervical groups. This glandular involvement may appear as early as the first day. Sometimes it is slight and accompanied by very little tenderness; in the more advanced cases it may be severe, with the formation of “bull-neck”—a collar of matted and enlarged glands all around the neck. Suppuration is not likely to occur except in cases of mixed infection, where there may be sloughing of the infiltrated mass.

The toxic effect of the disease is also seen in the general symptoms which it causes. The *temperature* rises to 100 to 102° F. (37.8 to 38.9° C.) in the moderate cases, and up to 104° F. (40° C.) in the more severe ones, falling by lysis in both. The severe cases are accompanied by the usual manifestations of hyperpyrexia, and in young children occasionally by convulsions. The fever, however, is greatly modified by serum therapy.

The *pulse* and *respiration* correspond to the temperature, but often the pulse in children is much more rapid than the fever warrants. Pallor and apathy, prominent features of the disease, increase and indicate the effects of the toxin.

The *blood* shows moderate leukocytosis, the increase being in polymorphonuclear cells. Myelocytes are also present, especially in fatal cases. There is a marked reduction in the red blood corpuscles, which may fall as low as two million or even five hundred thousand, with a corresponding diminution in the hemoglobin percentage to 10 or 30 per cent. Patients with the latter symptom recover much more slowly than those with the former.

Albuminuria is very common, so much so that it is considered a part of the symptom-complex of diphtheria. It may appear at any time from the third to the seventh day, in amounts varying from a slight trace to a considerable percentage, and may persist for several weeks. Acute nephritis with hyaline and epithelial casts is rare, although it may occur.

With the early administration of antitoxin in sufficient dosage, the progress of the disease is promptly arrested. The membrane begins to separate, falling off piecemeal and also disappearing by absorption, which begins at the margins and is completed in two or four days, accord-

ing to the size of the membrane, sometimes leaving a delicate grayish infiltration which persists for a few days more. The mucosa, relieved of the membrane, appears markedly red. The fever begins to subside within 24 hours after the injection and reaches the normal on about the third day, when the patient begins to feel comparatively well. Sometimes mild as well as severe cases will give negative cultures almost immediately after the parts become normal in appearance. Others, even very mild ones, will continue to give positive cultures indefinitely for weeks or even for months. There is nothing in the local condition to account for the one or the other phenomenon.

Without serum therapy the course of the disease, in favorable cases, is protracted over a period of from eight to 14 days. The membrane adheres firmly, generally spreading over the entire throat and often involving the neighboring structures. The difficulty in swallowing is intense and agonizing. Prognosis is uncertain. Although recovery may take place, there is always the danger of laryngeal involvement with stenosis, as well as of the sudden development of heart symptoms leading to death; death may occur at the end of the second week from heart complications, nephritis or bronchopneumonia.

SECOND ATTACKS.—An attack of diphtheria does not confer the same immunity against the disease as results after other acute infections, such as smallpox, scarlet fever and measles. Relapses may take place during convalescence, or the disease may recur in three or four weeks or any time after recovery. As a rule, the relapse (occurring during or shortly after convalescence) is not so serious as the original attack, although death may occur during a relapse. Second attacks or even third attacks at remote periods after the first one are not at all uncommon and are dependent upon the individual disposition to the disease and the opportunity for infection.

It seems reasonable to believe that subsequent attacks are especially liable to occur following cases which have been promptly and effectively treated with adequate doses of antitoxin. In such instances the toxin is neutralized before sufficient time has elapsed to produce any degree of active immunity.

Diagnosis.—There is perhaps no medical condition in which early diagnosis entails a greater responsibility than in diphtheria or cases that suggest diphtheria. Inasmuch as we have at our disposal a prompt and effective means of controlling diphtheria in its early stages (within the first 24 to 36 hours), it is not too much to say that when confronted with a suspicious case the doctor, unless he is one hundred per cent sure that it is not diphtheria, should at the first visit administer antitoxin in full dosage. This is essential for the salvation of the patient, for the protection of the public and for the reputation of medicine in general and of the individual physician in particular. In view of this it seems almost superfluous to discuss the diagnosis of diphtheria, more especially since the clinical picture and the bacteriologic findings often fail to harmonize, and much valuable time is lost in arriving at a diagnosis. Therefore, to treat and then diagnose is the order of procedure to be observed in the presence of a sore throat or other symptoms which arouse the slightest suspicion of diphtheria, for the efficacy of serum treatment depends upon its early administration.

The clinical symptoms of diphtheria, as already enumerated, are sometimes so modified as to be misleading. In young children, for example, there is often little discomfort in the throat, and not until the glandular enlargement and the pharyngeal symptoms are marked will attention be called to the throat. Inspection of the throat, therefore, should be a part of the routine examination in all disorders of childhood.

In the diagnosis of diphtheria we can to some extent be guided by the age of the patient, the location and appearance of the lesions and the clinical manifestations of fever and albuminuria.

As regards age, it is well to remember that children do not often suffer from throat conditions such as tonsillitis, quinsy and other anginas with which diphtheria is likely to be confused, so that, provided scarlet fever and thrush can be excluded, any visible patching of the throat of a young child should be treated as diphtheria.

As to the location of the lesion, in diphtheria it generally affects the pillars of the fauces, the uvula or the soft palate. And, although Vincent's angina may often have to be considered, it is safe to act on the suspicion of diphtheria. Primary lesions of the buccal mucosa, while they may be due to thrush, should be considered as diphtheria until proved otherwise.

The true diphtheritic membrane is often described as pearly gray in appearance. But in reality the color is no index, since it is seen in every shade from a dead white, or a yellow, to even a deep black. While the adherence of the membrane and the raw surface that its removal often leaves may be taken as positive indication of diphtheria, the absence of these features cannot be relied upon as contraindicating the disease. It must be remembered that the diphtheritic membrane soon begins to separate spontaneously, and the case may come under observation at the time when the membrane is more or less easily detached. And as to the bleeding surface it leaves, it has been proved that even in cases of true diphtheria the deposit has been removed without leaving such a surface.

With regard to the other clinical symptoms, it is well to remember that the combination of low fever or even subnormal temperature with a patched but not painful throat and albuminuria is apt to indicate diphtheria, since in other throat conditions the temperature is usually high, and the throat painful. It is especially the low temperature together with albuminuria that should arouse suspicion.

DIFFERENTIAL DIAGNOSIS.—Faucial diphtheria is likely to be confused with *tonsillitis*, *quinsy*, *septic angina*, the *ulcerative sore throat of Vincent's angina*, *symphilitic angina*, *tuberculous angina*, *thrush*, *herpes* and, finally, *scarlatinal angina*.

Acute tonsillitis differs from faucial diphtheria in that the pain in the throat is more severe, there is more generalized redness, the temperature is high, the face flushed, the pulse full and bounding and the tenderness of the enlarged cervical glands much more marked. In fact, there is a preponderance of general, constitutional symptoms, especially pain in the head, back and extremities, not noted in diphtheria. The exudate of tonsillitis may very closely resemble that of diphtheria in its early stage, in that it may spread over a portion of the tonsils or the posterior faucial pillar. There may also be a superficial slough which strongly suggests diphtheria, but the fact that the membrane is easily removed and when separated rarely leaves a bleeding surface is

evidence in favor of tonsillitis. Very often, however, the differentiation is possible only after repeated bacterial examination.

The differentiation from *quinsy* should as a rule be easy, since supuration of the tonsils in diphtheria is most unusual, and the tonsillar enlargement in quinsy gives the back of the throat a one-sided appearance, while the soft palate on the affected side is apt to protrude forward and downward. With these distinguishing signs, diphtheria can generally be excluded, even though there be a small amount of exudate present. But often after a tonsillar abscess has been incised the resulting grayish wound may resemble a diphtheritic membrane. It differs from the latter by the fact that the membrane does not spread and that the tonsillar enlargement is peripheral only. In some instances confusion may be due to the thin exudate that settles on the tonsils when the abscess ruptures high up and at the back of the tonsils, and from which pus exudes at every attempt to swallow; sometimes the film assumes the character of a well-organized membrane. Inspection of the throat is difficult because the patient is unable to open the mouth, the latter symptom being an almost infallible indication of quinsy, and often in such circumstances a diagnosis of diphtheria will be made. Giving antitoxin in such a case can do no harm, but inspection (when possible) and the ease with which the membrane wipes off should solve the question. Quinsy can also often be recognized by a fluctuating mass, felt on palpating with the fingers. In some rare instances, however, true diphtheria is also accompanied by an excessive amount of peritonsillar inflammation and by other symptoms of quinsy which make differentiation difficult. This further emphasizes the importance of prompt administration of antitoxin in ample dosage.

Vincent's angina is usually unilateral and is characterized by a greenish-gray membranous formation on an ulcerative base which, like the diphtheritic membrane, is not easily wiped off, while a strong fetid odor from the mouth may also suggest diphtheria. It differs from the latter in that the membrane is not influenced by antitoxin, persists for a longer time (about fourteen days), that local symptoms and fever are not marked, and finally in its bacteriology. Spirilla and fusiform bacilli are present in such large numbers as to suggest pure cultures. It is important to remember, however, that spirilla and fusiform organisms may often be associated with diphtheria bacilli. They are sometimes so numerous as compared with the latter, if studied without a culture, as to lead to a false diagnosis of Vincent's angina. Therefore, where there is the least doubt a search for diphtheria bacilli should be included in the bacteriologic examination of smears from a suspected case of Vincent's angina.

Syphilitic ulceration in the throat also frequently suggests diphtheria, especially since the removal of the slough may cause slight hemorrhage and the temperature may remain normal. But the absence of constitutional symptoms, the location of the lesions well forward in the throat, and usually also on the hard palate, the character of the slough, which is apt to be depressed with the edges of ulceration well defined, together with the history of the case, the possible presence of syphilitic lesions elsewhere, the failure of diphtheritic serum therapy and the results of specific treatment, will generally point to the true nature of the disease.

In *tuberculous ulcerating sore throat*, the chronicity and the presence of tuberculous lesions elsewhere should render differentiation easy.

In differentiating faucial diphtheria from *thrush* it should be noted that the patches of thrush are milky white in color, and occur in almost any situation, even on the tongue and lips. But they are not surrounded by inflammation and are easily wiped off, while the underlying tissue is normal. Under the microscope the patches reveal mycelia and spores.

In *herpes* the tonsils are often the site of numerous vesicles which on rupturing leave grayish sores. But unlike diphtheria, herpes is nearly always accompanied by violent headache and also by the presence of lesions on other parts of the buccal mucosa, especially the lips. Epidemics of herpes and diphtheria are often concurrent, so that the presence of lesions on the lips should not rule out diphtheria, and the proper precautions should be instituted.

The chief source of confusion of faucial diphtheria is with *scarlatinal angina*. At first thought, especially to the inexperienced, this may seem incredible, since the typical case in each disorder presents distinct and widely divergent symptoms. But hospital experience teaches that confusion often occurs, and with disastrous results. Differentiation is of the utmost importance and, indeed, presents one of the most vital problems in fever hospital management.

The confusion occurs, not only in those aberrant cases of scarlatina in which the exanthem is so slight as to escape detection, and where desquamation has not yet set in, but also in the more regular case where the throat symptoms during the first two or three days may be highly suggestive of diphtheria. The uncertainty is furthermore enhanced by the very frequent association of the two diseases.

One of the most reliable symptoms in those cases which are examined on the fourth to the sixth day of the disease is the presence of the "strawberry tongue" and its tendency to desquamation; this can usually be taken to indicate scarlatina. In other words, in borderline cases a pale, thinly-coated tongue, showing no tendency to desquamation after two or three days, is almost proof positive that the case is not scarlet fever. Another point of differentiation is the fact that in scarlatina the tonsils and the uvula are much redder than in diphtheria, the infiltration often extending to the hard palate, while the exudate which covers the tonsils in the form of small white specks consists of pulaceous debris which is easily wiped off and contains neither fibrin nor diphtheritic bacilli. The presence of the scarlatinal exanthem will, of course, clinch the diagnosis. The study of the palate, also, is often of much help in diagnosis. In scarlet fever the palate is quite consistently reddened and shows distinct elevations or puncta. This is rarely seen in diphtheria, so that in doubtful cases a pale, smooth palate is strong evidence, in fact almost positive proof of diphtheria.

In the septic cases of scarlet fever with severe throat symptoms, the patient is flushed and restless, in marked contrast to the pallor and apathy that characterize diphtheria.

As to other early symptoms, neither vomiting, rhinorrhea nor glandular enlargement is of much aid. Vomiting, although quite a constant initial feature of scarlatina, may also be present in diphtheria; rhinorrhea is a feature of both diseases, and the glandular enlargement in severely septic diphtheria may be as pronounced as in scarlatina. On the other hand, albuminuria is not apt to appear as early in scarlatina as in diphtheria, and may thus serve in differential diagnosis. In some

instances the differentiation cannot be made until the third week of the disease, when the typical pinhole desquamation, or symptoms of nephritis or of arthritis will settle the doubt, if it has not already been cleared up by bacteriologic examination.

The differentiation of laryngeal diphtheria from nondiphtheritic laryngeal obstruction or *croup* sometimes presents considerable difficulty. If, during the course of faucial or nasal diphtheria, symptoms of stenosis set in, the diagnosis is plain. But in cases of primary laryngeal diphtheria the differentiation is not easy. It is therefore a safe rule to consider symptoms of croup in a young child as suspicious, and to institute serum therapy at once without waiting for bacterial confirmation, more especially so since we know that reliance can be placed only upon positive and not upon negative evidence, and that in primary laryngeal diphtheria negative cultures mean less than in other forms and are therefore misleading. In some instances, after a careful examination the suspicion of diphtheria will fall away, and it will be realized that the obstruction is due to some nondiphtheritic condition, such as laryngospasm, acute simple laryngitis, laryngismus stridulus, edema of the glottis, retropharyngeal abscess and influenza. In these the voice remains unchanged and respirations between attacks normal, whereas in laryngeal diphtheria, hoarseness and loss of voice are practically the rule.

Acute simple laryngitis, which often sets in with hoarseness and a croupy cough, is not accompanied by persistent stridor and contraction of the soft parts; it yields readily to treatment, such as placing the child at the open window in order to give it plenty of air, and the application of heat (hot flannels, or cloths wrung out of hot water). The history of a tendency to attacks of "croup," especially at night, the absence of constitutional symptoms and of a known exposure to diphtheria should rule out the latter. But well-marked and persistent dyspnea should arouse suspicion, and no time should be lost in applying serum therapy.

Special attention is directed to the importance of differentiating an attack of "croup" during the course of *measles*. Laryngitis, which often appears in measles before the eruption breaks out, may be associated with marked inflammation and swelling of the laryngeal membrane leading to symptoms of obstruction with stridor and contraction; often small ulcerations will be found on the epiglottis. While the appearance of Koplik's spots is a reliable sign of measles and demands the isolation of the patient, any doubt as to the true nature of the trouble should be sufficient indication for giving antitoxin.

Very often the convulsive spasms of *laryngismus stridulus* suggest laryngeal diphtheria. But it can be distinguished by the more or less prolonged apnea followed by crowing gasps after the spasm relaxes and frequently also by strabismus and actual convulsions. Furthermore, it rarely attacks children over two years of age and is generally a manifestation of rickets. Any of these signs should rule out diphtheria.

The most serious affection which is likely to be confused with laryngeal diphtheria is acute *edema of the glottis* occurring in connection with inflammatory or suppurative processes localized in the larynx or its vicinity, such as erysipelas, which may extend from the pharyngeal mucosa to the larynx and induce sudden obstructive symptoms; or severe phlegmonous angina may lead to acute edema of the glottis. Examination

of the throat and the larynx and study of the history of the case will generally indicate the correct diagnosis.

Retropharyngeal abscess may also often suggest laryngeal diphtheria. But the difference appears on inspection of the pharynx, which often shows a fluctuating mass that can be seen or be felt with the fingers; the characteristic voice also serves to differentiate the two conditions. Furthermore, the onset is prolonged, extending over several days or a week; the patient throws back the head for the better admission of air; there is considerable difficulty in swallowing, and the swelling of the neck is much more marked than in diphtheria. The voice is characteristic, best described as a harsh, guttural pharyngonasal sound, which once heard is never forgotten. The entire condition also shows evidence of a prolonged wasting illness.

During the severe epidemic of *influenza* in the fall of 1918, many cases were sent to hospitals with a diagnosis of laryngeal diphtheria, but which proved to be influenza with laryngeal symptoms so marked as to require intubation. The differentiation in favor of influenza rests upon the more pronounced constitutional symptoms, especially the prostration, which is much greater than in primary laryngeal diphtheria, also upon the greater tendency to develop pneumonia, the frequent and violent coughing resulting in auto-extubation, and finally upon the failure to respond to serum treatment as evidenced by the necessity of re-inserting the tubes in those patients who survive; this, together with the danger of pulmonary involvement, renders the prognosis of these cases very unfavorable.

Other conditions that produce symptoms of laryngeal obstruction are the *edema* resulting from serum sickness, *papilloma of the larynx*, *acute swelling of the faucial tonsils* and more rarely *bronchial glandular tuberculosis*. A careful examination, together with the history of the case, should make the distinction clear in such instances.

Hypertrophy of the thymus is variously reported as simulating diphtheritic laryngeal obstruction. The chronic condition of the illness, the absence of hoarseness, except as the attacks recur, and roentgen-ray evidence will point to the true cause of the trouble.

Differential diagnosis in many instances, as we have seen, can be made only after bacteriologic examination. In urgent cases this can often be promptly obtained by the study of smears of the false membrane stained with methylene blue or carbolfuchsin. If the case is diphtheria the specimen will show, in addition to fibrinous threads and the usual buccal flora, a few bacilli strongly suggesting the Klebs-Löffler organism. But the absence of the latter cannot be taken as reliable evidence that the disease is not diphtheria, so that cultural tests will have to be the deciding factor.

To obtain the material for a culture, a swab is firmly rubbed along the edges of or under the membrane, care being taken not to touch the teeth or the tongue. The swab is then rubbed on the culture medium—Löffler's blood serum—and incubated for 12 or 18 hours at body temperature. In positive cases the culture will then be found to consist of streptococci, the usual buccal bacteria and colonies of diphtheria bacilli. The last, after being collected on a platinum wire, are placed on a slide and stained with methylene blue (Löffler) for five minutes.

The protoplasm of the bacillus will take a blue stain and the granules a reddish-purple. The presence of the long or short organisms with

beaded ends, with the above method of staining, may be taken as positive evidence of diphtheria. This reaction, especially in young cultures, is sufficient for the general practitioner; sometimes the differentiation between the Hoffmann bacillus and the rare form of diphtheria bacillus that takes an even stain may have to be made. The Hoffmann bacillus, both in the smear and in the culture, appears as a short rod and is generally arranged in parallel lines. It takes an even stain, is not beaded, and occasionally has an unstained septum across its center. Its colonies are more opaque than the diphtheria bacillus and it does not cause acid formation in a glucose medium. It is best, however, when these distinctions are to be made, to submit the specimen to a trained bacteriologist.

After the culture of the diphtheria bacillus has been obtained the final test is then made by inoculation into the guinea-pig, which usually dies within 36 hours.

In view of this fact, and also because of the time consumed in obtaining a culture, it should be remembered always that, for safeguarding the public health, as well as for giving the patient the benefit of any doubt that may exist, the proper thing to do in a suspicious case of angina is to institute serum therapy at once, and then have the diagnosis clinched by bacteriologic evidence. This is all the more important inasmuch as neither positive nor negative cultures are absolutely reliable. It is known that the diphtheria bacillus may be present in the throat of perfectly healthy individuals and, as previously stated, that the first cultures may be negative in the presence of unmistakable clinical manifestations of the disease.

Complications and Sequelae.—Cardiac and paralytic manifestations are the most constant complications of diphtheria.

The poison elaborated by the diphtheria organism exercises its most powerful effects upon the heart, which is likely to be involved in practically every case of the disease. Indeed, some authorities regard the cardiac manifestations as part of the symptom-complex, but inasmuch as the symptoms do not usually appear until after the acute stage is passed, that is, after the first week, and generally not until the third or fourth week of the disease, it seems reasonable to regard them as a complication.

The mild heart symptoms are the same as those which accompany other infectious diseases—transitory arrhythmia and accidental murmurs. *Heart failure*, that dreaded complication of diphtheria, may occur suddenly at any time during the first two weeks of the illness, even in patients who have shown no marked signs of toxemia, or it may take place during the operation of intubation or tracheotomy. This early heart failure usually occurs where there is early palatal paralysis, although it is known to appear even before any paralytic complications have set in. Heart failure may also be progressive, manifesting itself by a gradual weakening of the pulse, which has been bad from the first. Death may come suddenly without warning at any time during the acute stage of the disease or even during convalescence in both the severe and the apparently milder cases.

As a rule, postdiphtheritic cardiac complications are preceded by foreboding signs such as unusual pallor, apathy, nausea and the fatal symptom of vomiting. The latter may be repeated for a few days after the onset, but usually there is epigastric constriction and pain together with precordial discomfort. On percussion, the heart shows some dila-

tation, while auscultation reveals dull heart sounds with an occasional accidental murmur. The blood pressure falls, the pulse is small, soft, slow and irregular. The patient, retaining consciousness during this time, may pass away very gradually, or, as more generally happens, he may fail to rally from one of the recurring attacks of syncope.

The danger of heart failure persists as long as there are signs of paralysis. In the absence of the latter the patient may generally be considered out of danger at the end of the fourth week; but late paralysis occurring after that time is not unknown and must be taken into consideration in the treatment of convalescence and in the early days after convalescence.

Among the direct results of the cardiac weakness are enlargement of the liver, and kidney involvement, sometimes with ascites; in rare instances one also finds thrombosis in the dilated heart with development of secondary emboli as in the brain, the larger vessels of the extremities, the abdominal aorta or in the lungs.

A peculiar characteristic of the diphtheria toxin is the production of *paralytic phenomena* which are pathognomonic of the disease. Early manifestations may be seen in the severe cases on the third or fourth day after onset in the form of paresis affecting the palate. But the complication is generally spoken of as postdiphtheritic paralysis since it is more apt to set in during the first and second week of convalescence—after the membrane has separated. It is more likely to affect children than adults and is more frequent following faucial and nasal diphtheria than when the lesions have been confined to the larynx and the trachea. The incidence of postdiphtheritic paralysis varies with the virulence of a given epidemic. Some authorities believe that it has become much less frequent since the introduction of serum therapy, while others claim that it has increased. The latter theory may be due to the greater attention and accuracy of observation accorded these phenomena, which were formerly often overlooked. But the increased frequency is more apparent than real, since it is probably due to the greater percentage of recoveries (owing to serum therapy) from the severe type of the disease, which is more apt to develop paralytic manifestations than the milder cases. The mild type, however, is not entirely immune; in fact, severe paralysis with death has been known to follow after what seemed to be a very mild case of faucial diphtheria.

The paralysis usually begins at the site on which the diphtheritic membrane develops. Accordingly, the soft palate is most frequently affected. Even in those cases in which other paralyzes take place later in the disease, such as accommodation paralysis, ataxia, paralysis of the extremities and the respiratory muscles, the earliest manifestations are those which affect the soft palate.

Palatal paralysis may occur very early in the disease (about the fourth day), and is then due to muscular changes. Later on palatal paralysis is due to degeneration of the affected nerves (the palatine). The precocious type should be taken to predicate a more severe course of the diphtheria; it is often accompanied by cardiac symptoms and by the graver forms of paralysis.

The first signs of paralysis of the soft palate are a nasal twang to the voice and difficulty in swallowing, fluids being returned through the nose owing to incomplete closure of the nasopharynx. Inspection will show a lax condition of the pharynx and the uvula during phonation, and

there may also be diminished sensibility of the palatine mucosa. Isolated palatal paralysis, as a rule, persists for two or three weeks, rarely beyond that time. The first sign of regression is improvement in the act of swallowing, followed later by resumption of the natural voice. Palatal paralysis is associated with paralysis of one or more muscles in about sixty per cent of diphtheria cases; it is most often associated with that of the ciliary muscles.

Ciliary paralysis is next in frequency to the palatal affection. The patient usually complains of difficulty in accommodation; although when he starts to read the letters appear plain, they soon become blurred. This loss of accommodation is a comparatively early manifestation. It may and usually does appear during the third week of the disease, but may not set in until the seventh or eighth week; it rarely persists longer than five, the average being about three weeks. In young children, unable to read, this complication may often be missed. The phenomenon is occasionally accompanied by abductor paresis manifested by strabismus; less often it is associated with ptosis, and in rare instances with optic neuritis.

The *extremities* are involved in postdiphtheritic paralysis almost as often as the muscles of accommodation, and in about one-third of all cases the paralysis is limited to these regions. The lower members are usually the first to be affected, the symptoms often beginning with a creeping sensation and weakness in the legs, ataxic gait, and diminished or abolished patellar reflexes. There are often some disturbance of station, anesthesia and hyperesthesia, especially in the distal portions of the member. Sometimes the process is arrested at this stage of "acute ataxia," and normal conditions return in from four to six weeks. In more severe cases the ataxic symptoms are followed by paresis and degenerative paralysis of individual muscles (peroneus, etc.), the patient being unable to support the body. There is also flaccid paralysis with partial degenerative phenomena and associated involvement of the upper members as well as of the trunk and the nape of the neck. Even in the most pronounced cases recovery is the rule, especially after massive doses of antitoxin. But convalescence is often prolonged over two or three months, or more, and in some rare instances, especially after paralysis of the ulnar, contractions may be permanent owing to atrophy of the *interossei*.

The most distressing and most fatal type of postdiphtheritic paralysis is that of the *respiratory muscles*, the intercostals, especially of the diaphragm. In isolated paralysis of the thoracics the diaphragm remains almost immobile during respiration, the act being carried on chiefly by the intercostal muscles. Paralysis of the diaphragm is manifested by the absence of abdominal arching during inspiration, while if there is also a paresis of the abdominal muscles, expiration becomes increasingly difficult. Often there is an associated paralysis of the thorax which increases the distress and is frequently accompanied by dyspnea and paralysis of the larynx, necessitating tracheotomy. Death ensues either from respiratory paralysis or from aspiration pneumonia. Jochman observed this distressing generalized paralysis in 3.8 per cent of 130 cases of postdiphtheritic pareses.

Paralysis of the *pharyngeal muscles* may also take place without generalized paralysis. It can be recognized by loss of voice, with a peculiar,

high-pitched, rattling cough, a tendency to splutter while eating, and inability to swallow and to clear the throat. Food may pass into the larynx, producing complete sudden obstruction, or pneumonia may result from particles of food entering the lungs. Ker reports a case in which pulmonary tuberculosis developed after this type of "food pneumonia." The condition is serious because of the danger of the patient's choking to death. In severe diphtheria this type of paralysis may occur early and in conjunction with palatal paresis. But it usually takes place during the fifth to the seventh week of the illness and generally disappears in about ten days.

In addition to these—the more frequent and important postdiphtheritic paralytic manifestations—paralysis of almost any nerve, either isolated or in association with other nerves, may result from the effects of the diphtheria toxin. Fortunately, these pareses are rarely simultaneous but follow each other, the one appearing as the other improves. The prognosis is generally favorable, recovery being the rule.

A much dreaded and often fatal complication of diphtheria, which is especially liable to occur in the laryngeal cases, is *bronchopneumonia*. While it is mostly due to some other septic infection, particularly streptococic, it may sometimes be purely diphtheritic in character. The symptoms are persistently high temperature, rapid respirations and more or less coughing. Fine crepitations may sometimes be made out, but more generally the physical signs are obscured owing to intubation or tracheotomy. In spite of the relief to the laryngeal obstruction afforded by the latter, the condition may spread, leading to death in two or three days. In the favorable cases, however, temperature and respiration subside gradually, reaching the normal in from ten days to three weeks.

It may also happen that the ear becomes infected by way of the eustachian tube, resulting in *otitis media*. The discharge, at first clear, soon becomes purulent and may also be hemorrhagic. It generally subsides completely and is very rarely so severe or extensive as to lead to mastoiditis; some authorities claim that it never occurs, but it has been observed in two cases in an experience of eleven years covering very nearly 21,500 cases.

The toxic effects of the disease are also seen in the emaciation of the patient, increasing almost to cachexia, and in the *nephritis* which sometimes appears as a complication of severe cases of diphtheria. Albuminuria, as we have seen, is commonly regarded as one of the symptoms of the disease, but in some instances, not necessarily only the severe cases, there is a true acute parenchymatous nephritis with excretion of large amounts of albumin (8 to 10 per cent), casts and leukocytes. As a rule, however, severe malignant diphtheria is accompanied by constant albuminuria of 2 to 3 per cent. The urinary output is reduced, but not so much as in scarlatina, specific gravity is increased and urobilinuria is not uncommon. The urine is rarely bloodstained. Diphtheritic albuminuria in the favorable cases (those that do not succumb to heart or other complications) usually subsides in two weeks, and in the lighter cases in two or three days; it very rarely develops into chronic nephritis.

Association with Other Diseases.—Diphtheria is liable to be associated with one or more of any of the other acute infections, the most frequent combination being *scarlatina*. It may set in early in the scarlet

fever, but in reality this is rather unusual. The pseudomembrane of early scarlatinal angina is often so much like true diphtheria that, judged by the membrane alone, differentiation is almost impossible and can be made only after repeated cultures. It is this type which furnishes a large percentage of so-called, but not actual, mixed infections. The fact that a positive culture is occasionally obtained from these cases does not necessarily indicate true diphtheria, since it may represent a diphtheria carrier who happens to have developed scarlet fever. At the same time, it is best to give these patients the benefit of any doubt that may exist and to administer antitoxin at once. This is especially advisable in fever hospitals, inasmuch as it at once wards off the danger of diphtheria, at least during the acute stage of scarlet fever, and thus gives the patient a better chance of combating the scarlatina, which is not in any way influenced by the antitoxin.

It is from the third to the sixth week of the scarlet fever that the patients show the greatest susceptibility to diphtheritic infection. This cross infection is more liable to occur in hospital than in private practice, since it may happen that a mild case of diphtheria will go undetected and thus become the source of infection for other scarlatinal cases. The course of a diphtheritic infection developing in these cases differs in no way from primary diphtheria, except that the prognosis may be unfavorably affected owing to the weakened condition of the patient. At the same time, when the cross infection does occur in a fever hospital the prognosis is more favorable than in private practice because of the constant vigilance that prevails in a well-conducted hospital, which permits of prompt recognition as well as prompt treatment with antitoxin. On the other hand, scarlet fever developing on diphtheria may present an unfavorable outlook, inasmuch as the already damaged condition of the mucous membranes, especially of the throat, is apt to conduce to the severer manifestations of scarlatinal angina.

Measles also seems to show a particular predisposition to diphtheritic infection, the catarrhal condition presenting a focus of minor resistance. In the majority of cases the diphtheria accompanying measles is of the laryngeal type. The croup may be preceded or accompanied by nasal diphtheria. Loss of voice, dyspnea and contraction of the soft parts of the chest during the course of measles should at once arouse suspicion and call for immediate serum treatment. The prognosis of the combination is grave on account of the danger of bronchopneumonia.

The same danger is present when diphtheria develops during *whooping cough*. When thus associated the onset of the diphtheria is apt to be insidious, the pharynx remaining clear, and the first signs of the added trouble being obstructed breathing or a catarrh in one or both nostrils with a profuse mucopurulent discharge, cultures of which reveal the diphtheria bacillus. The diphtheritic process, after persisting for some days, often spreads to the pharynx, resulting in an acutely serious condition; or faucial or laryngeal diphtheria may also develop without the primary nasal invasion.

Diphtheria sometimes develops during *typhoid fever* and is apt to be mistaken for laryngeal manifestations of the latter. Symptoms or laryngeal stenosis during typhoid fever should arouse suspicion and, unless diphtheria can be absolutely ruled out, should be combated by the prompt use of antitoxin.

The association of *varicella* and diphtheria is not uncommon but is of little import as affecting the diphtheria. *Acute anterior poliomyelitis* with diphtheria is a more serious combination. During the epidemic of the summer of 1916 the two diseases were often associated and proved fatal in a number of instances.

Clinical Varieties.—Variations may occur, from the *severely malignant type* of diphtheria which yields neither to serum therapy nor to cardiac stimulation and runs a fatal course in three or four days, to the *less malignant type*, which, with prompt administration of antitoxin, may result in recovery, but in which the postdiphtheritic manifestations delay convalescence and continually threaten life, and to the *benign catarrhal type* presenting merely a catarrhal or follicular angina, diagnosable mainly by bacteriologic cultures.

In the *malignant type* the invasive symptoms may be insidious, and the throat unobtrusive, although examination on the first day will reveal the presence of the typical membrane; or the invasion may be sudden and stormy. The membrane rapidly develops on the tonsils, the uvula and the soft and hard palate, and may extend to the nose, from which visible particles often protrude or are emitted on blowing the nose; it may also settle around the anterior nares and on eroded surfaces around the corners of the mouth. Hemorrhagic tendency is a feature of the very severely malignant faucial diphtheria and extends into the skin surfaces, especially those of the extremities, the trunk and the forehead.

The patient's appearance is marked by extreme pallor, apathy and stupor. He breathes through the mouth, emitting a characteristic fetid odor. The membrane spreads widely over the fauces and tonsils and is of a dirty gray color with dark, hemorrhagic central areas.

The pulse is rapid, and extremely soft and irregular. There is often a tendency to vomit, a very bad prognostic sign. Death generally results from cardiac failure and may be sudden, due to the strain of vomiting, or it may be slow, occurring as late as the second week, or later, accompanied by manifestations of severe toxemia, paralysis of the heart or of other muscles, or a low form of bronchopneumonia. The fever in the more favorable cases may rise to 102° F. (38.9° C.), but it soon falls and remains around 100° F. (37.8° C.). The liver and the spleen are swollen, and kidney involvement is manifested by albumin and casts in the urine. On about the sixth day the membrane begins to separate and the temperature soon returns to normal. But the patient is listless, emaciated, pale and weak. The edema of the neck subsides and the swelling and tenderness of the glands disappear. The membrane may separate in a mass, although sometimes it fades away so gradually that it is difficult to determine just how long the process lasts.

Convalescence is slow and often protracted by postdiphtheritic manifestations, especially paralysis of the muscles of the soft palate or of the pharynx, and by cardiac arrhythmia.

The *benign catarrhal type* of faucial diphtheria is diagnosable mainly by bacteriologic cultures. It generally runs a rapid course; although the temperature may rise to 102.2° F. (39° C.), it nearly always subsides in two or three days. This type may, however, develop into laryngeal croup, so that it is imperative to give all cases of angina developing in a diphtheritic environment antitoxin treatment.

In addition to this mild variety of faucial diphtheria there is an aberrant type which results from secondary pyogenic infection and which

may lead to severe parenchymatous tonsillitis in which the tonsils are covered with the false membrane, and the mucosa of the soft palate and of the hard palate is red and edematous, interfering with respiration and with swallowing. The tonsillar swelling usually subsides and only rarely is there abscess formation which, if it occurs, necessitates incision and drainage.

Extension of the diphtheritic membrane from the fauces to the nose occurs in about twenty per cent of cases; but *nasal diphtheria* may also be a primary manifestation of the disease. This type is particularly dangerous and is more generally fatal than the faucial type. Because of the difficulty of its early recognition, treatment is apt to be delayed, unless the membrane happens to localize within the nostril and can be seen on examination. Otherwise there is nothing that would arouse suspicion that the rather severe nasal catarrh, with more or less marked constitutional symptoms, is due to the presence of the diphtheria bacillus on the nasal mucosa, until the advance of the disease leads to unusual prostration, and the discharge from the nose assumes a serosanguineous character; often the discharge of a fragment of membrane is the first hint of the true nature of the disease. By this time the toxemia will already have had a chance to get in its destructive work. If, however, simple nasal diphtheria is recognized early and is promptly treated with antitoxin there is no reason why it should be any more dangerous than the simple faucial disease. With a history of exposure to diphtheritic infection, every discharging or dirty nose should be considered as a probable case of diphtheria and should have antitoxin treatment at once.

Sometimes infection is carried by way of the eustachian tube to the ear, which presents inflammatory symptoms and, at times, contraction of the ear drum. The onset of *diphtheritic otitis* is usually insidious, not making its appearance until the faucial or pharyngeal diphtheria is on the wane. The symptoms are gradually increasing pain in the ear, often progressing quickly to perforation of the ear drum, and the discharge of a seropurulent or sanguinopurulent secretion. The prognosis of diphtheritic otitis is generally favorable; it rarely develops into mastoiditis and hardly ever leaves any trace of impaired hearing. Diphtheria may also attack the tongue and the mouth, but the condition is very unusual.

Laryngeal diphtheria or croup, like the nasal variety, is dangerous because of the difficulty of inspection and the consequent delay in serum treatment. The infection may be primary, or it may result from infection from faucial diphtheria. In the primary type the usual constitutional symptoms are often wanting, either because death may ensue from obstruction before the symptoms of toxic absorption have had a chance to appear, or because the larynx, compared to the pharynx, possesses a weaker power of absorbing toxins.

Laryngeal diphtheria is more apt to occur in very young children than in older ones, and, in view of the narrowness of the infantile larynx and the tendency to convulsions, laryngeal croup is always a serious matter in a young child. As a rule, the first indication of the trouble is huskiness of the voice with a typical barking, "brassy" cough, soon succeeded by loss of voice, inspiratory stridor, recession of the soft parts of the chest, cyanosis, restlessness, and rapid, weak, irregular pulse.

Very often the condition is preceded by a cold in the head, of one or two days' standing, which differs very little from an ordinary rhinitis,

except that the diphtheria bacillus will be found in the secretion; or the discharge may be seropurulent and the resulting excoriation around the nose may arouse suspicion of the nature of the secretion.

In older children and in adults extensive involvement of the larynx, the trachea and even the bronchi may occur unaccompanied by urgent symptoms; the patient may cough up membranous casts of these structures, and recovery may take place without any operative interference; in the severe toxic cases the patient dies, not from the diphtheria, but from cardiac failure.

Laryngeal diphtheria is the type most likely to develop when diphtheria supervenes as a secondary manifestation of one of the other acute infections, especially measles and whooping cough, the combination being particularly serious on account of the tendency to bronchopulmonary involvement presented by the primary, as well as by the secondary—the laryngeal—diphtheritic infection.

Bronchopneumonia, in fact, represents one of the great dangers of diphtheria of the larynx, either through invasion of the diphtheritic organism or from secondary pyogenic infection. Very often the complication is the direct cause of death, and at autopsy in such a case the membrane will be found on the trachea, the bronchi and even on the bronchioles. During life the membrane may be coughed up, although this is not as usual now as formerly, before the introduction of antitoxin, and occurs only in advanced and neglected cases. Sometimes the separation of a larger piece of membrane in the trachea or larynx may cause suffocation, which can be relieved only by immediate tracheotomy.

In most cases tracheotomy, if performed between the second and the fourth day, and the prompt administration of antitoxin lead to a rapid regression of the distressing symptoms. The fever subsides in two or three days, the diphtheritic process is inhibited, and particles of membrane are coughed up through the tube or cannula; generally the tube can be removed in two or three days.

In cases that do not come to treatment until the fifth or the sixth day, tracheotomy may relieve the local symptoms, but serum therapy instituted as late as that will scarcely modify the systemic effects of the toxemia, especially on the heart, so that the condition generally develops the severely malignant picture of diphtheria, ending in death. This is because the toxin of the diphtheria bacilli is no longer confined to the blood stream, and therefore cannot be neutralized by antitoxin even though it may be injected intravenously.

Tracheal diphtheria is the type in which the exudate and the inflammation are below the glottis; the voice is then, of course, not affected and the cough will not be croupy. The symptoms of obstruction, however, may be just as marked as in laryngeal diphtheria. The temperature remains elevated, especially if the lungs are involved, but when the laryngeal and tracheal affection is associated with the faucial and nasal types of diphtheria, the temperature remains consistently normal unless there is pulmonary involvement. Adenitis is present only when the laryngeal infection is an extension from the throat and nose.

As already indicated, the diphtheritic membrane may develop anywhere on abraded mucous or skin surfaces. *Cutaneous diphtheria* is more common among children than among adults, and most frequently develops on the anal and genital regions in the form of small ulcers which

generally heal quickly, or in the form of a membrane with considerable edema of the surrounding parts. The membrane may develop on the conjunctiva, either directly or from infection from the faucial or nasal type of the disease. The eye symptoms in such cases vary according to the deep or superficial character of the affection. In the presence of diphtheria elsewhere, any eye symptoms should receive attention.

Wound diphtheria results from infection of a wounded surface either from scratching or from contagion from a case of diphtheria. Postdiphtheritic paralysis is not unusual in such cases, and it is interesting to note that the paralysis begins in the affected parts, as, for example, paralysis of the thumb when that member has been the site of infection. The fingers are often infected, especially in young diphtheritic patients who are apt to put the fingers into the mouth; often in this way faucial diphtheria develops from transference of the membrane that has developed primarily on the fingers; and the physician's fingers, while performing intubation, may be infected in this way through some slight wound. The result is usually a more or less painful bleb which bursts and results in a sore covered with specks of diphtheritic membrane.

Treatment.—A logical sequence of topics in the discussion of diphtheria would require treatment to precede diagnosis, for, as has been already indicated, *to treat and then diagnose* is the one safe method when the physician is confronted with a throat which arouses the slightest suspicion as to its innocent nature. Conformity, however, demands that treatment be considered at this time.

PROPHYLAXIS.—The desirability of actively immunizing all children is no longer controvertible. It has not only been responsible for a marked reduction in morbidity and mortality in communities where it has been systematically applied, but in some it has actually eliminated diphtheria for as long as three or four years. It may now be regarded as being as effective as vaccination against smallpox or typhoid fever.

While credit is given to Theobald Smith for first suggesting active immunization by a toxin-antitoxin, von Behring, whose name will endure for all time as the discoverer of the antidiphtheritic serum, was the first to put it to practical use. His preparation was said to have been the undiluted toxic broth, with its toxin nearly neutralized by antitoxin. He never, however, gave a clear explanation of how he prepared or standardized it, and the breaking out of the war delayed further study and its use in Europe.

Park and the late Zingher were the first in America to appreciate the value of active immunization; and by the Schick test they were able to determine the susceptibility of children, and by a retest to note the changes in the human response to injections of toxin-antitoxin. They demonstrated that immunity developed in about 85 per cent of those receiving three injections of their 3 L + preparation at intervals of one week, and by 1917 they realized that it lasted in the majority of cases for at least several years. They also tried intervals of two weeks, but the results were only moderately better.

In 1918, Park and his associates began an extensive campaign to immunize the whole child population of the city of New York. Their earlier work was confined chiefly to children of school age, because parents were unwilling to have the injections given to babies or young children. Severe systemic and local reactions about this time prompted

them to dilute the toxin before adding antitoxin, and they found that when as little as 0.1 L + dose of toxin was given in the injections, the immunizing effect was as great as when 3 to 6 L + doses were used. Smaller amounts of toxin were less immunizing. They soon standardized their preparation, on finding that the maximum effect was possible when the toxicity in the human dose killed a 250-gram guinea-pig in about four weeks. This new preparation gave much less local reaction in children of school age and has since become recognized as being the standard toxin-antitoxin preparation.

The latest report from New York City is that more than 500,000 school children have been given toxin-antitoxin, and owing to an intensive drive to stamp out diphtheria, inaugurated by the Commissioner of Health, Dr. Wynne, more than 250,000 infants and pre-school children have received it. A very material reduction in the incidence of diphtheria has resulted.

It was soon realized that, while toxin-antitoxin was entirely effective in producing active immunity against diphtheria, it was also capable of causing severe reactions under certain conditions. First in importance was that the horse serum in the antitoxin part of the combination was a constant factor in the production of sensitivity or anaphylaxis in those already sensitive. To overcome this, antitoxin made from goat serum was used but was discovered to be impractical for production on a large scale.

On one occasion, 42 students in two colleges near a large New England city manifested severe local and constitutional symptoms as a result of the administration of toxin-antitoxin which had previously been exposed to very low temperature. An investigation revealed that prolonged exposure to a temperature below freezing is capable of causing the dissociation of the toxin from the combination. This episode and others inspired studies which led to the development of more stable and less toxic substances.

The most conspicuous effort in this direction came when it was found that formalinized toxin could be used to advantage in human immunization against diphtheria. Salkowski in 1898, and Lowenstein in 1924 described the action of formalin on soluble toxins. Glenny and Sudmersen in 1921, and Glenny, Allen and Hopkins in 1923 proposed that formalinized toxins be used. Independently of each other, in 1923, Glenny and Hopkins in London, Ramon in Paris, and Park and associates in New York began to test the value of toxoid preparations. In 1922, Ramon, at the Pasteur Institute in France, found that when antidiphtheritic serum was added in varying proportions to diphtheria toxin, a gradually increasing opalescence appeared, and after a few hours at ordinary temperature a definite flocculation became evident. This flocculation invariably appeared first in the tube in which toxin and antitoxin most nearly neutralized each other. Ramon considered this a specific reaction depending on the interaction of an antigen and its antibody. He further found that a toxin which has lost some of its toxicity by exposure at room temperature, or by other means, might retain its flocculating properties unimpaired.

While immunizing a series of horses for the production of antidiphtheritic serum, Ramon realized that the antigenic value of a toxin

did not depend upon its toxicity but was in close relation to its power of flocculation. This was the early development of what Ramon called *anatoxin*, but which has since been referred to as *toxoid* by English-speaking nations to avoid confusion with antitoxin.

Since Ramon's first announcement the literature has been voluminous in discussing toxoid, and there is every reason to believe from the various series of cases in which it has been used that it has partially, if not entirely, overcome some of the objectionable effects of toxin-antitoxin. As a result the trend seems to be toward toxoid as the substance of choice in the production of active immunization against diphtheria.

It has been shown, however, that toxoid may cause local and general reactions in older children. So far these reactions are apparently allergic in nature, and the opinion seems to be general that they are only unpleasant and never dangerous. On the other hand, young children very rarely give local or general reactions. This fact is most important because it is the pre-school child that is most susceptible to diphtheria, and it is in this group that any prophylactic measure finds its greatest usefulness. Mortality statistics seem to indicate that it is conservative to state that the immunity of one child for the first five years of life is equal in its effect upon the diphtheria death rate to the immunization of three school children.

Older children and adults may be immunized with toxoid, but it is recommended quite generally that a test for sensitiveness to diphtheria proteins be made before the immunizing injections are begun. This test may be carried out either alone or as a control for the Schick test. A small vial of diluted toxoid 1 to 20 is furnished by the manufacturers, and 0.1 cc. is inoculated intracutaneously, as for the Schick reaction. A local area of redness at the site of the inoculation more than one-half inch in diameter, appearing within three days, is interpreted as a positive reaction and indicates that the individual may give a local or general reaction to toxoid. These persons may receive toxoid in smaller doses, the first dose ranging from 0.2 to 0.5 cc. of the 1:20 dilution, depending upon the degree of reaction to the intracutaneous test. Subsequent doses may be given at intervals of two weeks and may be doubled if the local reaction from the preceding dose was not more than three-quarters of an inch in diameter. Reactions up to three inches in diameter call for a repetition of the first dose, while more severe reactions should cause the subsequent dose to be reduced. According to Defries these reactors are more easily immunized than individuals who are not sensitive to the diphtheria protein.

The extreme susceptibility of the pre-school child has long since eliminated the preliminary Schick test of immunity. For this reason, there seems to be no objection at all to immunizing pre-school children routinely with two 1 cc. doses of toxoid given at an interval of three weeks. However, it is well even in this group to test for sensitiveness if there is any reason to believe that the young child is allergic.

In older children it seems to be desirable to perform a preliminary Schick test, because it is equally well recognized, especially in urban communities, that the older children become increasingly immune through contact with carriers, or because of the fact that they may have been carriers themselves. The preliminary Schick test in older children has the additional advantage of separating those who are

allergic from those who may be immunized without fear of local or general reactions.

Ramon has succeeded recently in raising the intrinsic antigenic value of anatoxin (toxoid) by modification of the bouillon in which the toxin is elaborated. Using this improved toxoid in 1.5 and 2 cc. doses has resulted in the production of immunization in 100 per cent of a series of children. Not only has the Schick test remained negative, but the antitoxic titer has been higher than in children immunized in the usual way. Ramon also suggests that a fourth dose of toxoid be given one year after the initial series in all children who are still Schick positive. In 500 children immunized by Ramon, 5 per cent who remained positive were reduced to 0.2 per cent by a fourth injection. It is probable that the present procedure of using toxoid will be modified to conform with these later observations.

Schick Test.—In private practice the Schick test is usually performed with material obtained from one of the manufacturers of biologicals. Mix the bottle of saline solution with the bottle containing the small amount of diphtheria toxin. These amounts are put up by most manufacturers so that when they are mixed, 0.1 cc. contains $1/50$ of the minimum lethal dose (amount necessary to kill a 250-gram guinea-pig). The mixture of saline solution and toxin should be well shaken. The flexor surface of the forearm, where the test is usually performed, should be cleansed with alcohol, acetone, or ether. With a fine gage needle and glass syringe graduated in tenths of a cubic centimeter, 0.1 cc. of this mixture should be injected intradermally. It is very important that the injection be made intradermally and not subcutaneously. If the needle is intradermal the injection will result in an elevated wheal of the superficial layers of the skin. If this wheal does not appear the needle is subcutaneous and the test will be unreliable. Skill in the technic of performing this test may be acquired by practicing with sterile water. Obviously asepsis should be practiced in the performance of this test in order to secure uniformly satisfactory results. The reaction from this test usually appears between 24 and 48 hours and is at its maximum in from three to five days. If there is no reaction in 72 hours the test may be considered as being negative. At the end of one week, the area of a positive reaction resembles a bran-like flaking of the cracked epithelium. When the reaction is at its maximum there is a central indurated area surrounded by an areola of redness which may be an inch or more in diameter. It is important to distinguish the true reaction from the pseudoreactions which are found in a small percentage of older children and adults. For this purpose 0.1 cc. of a control solution should be injected coincident with the Schick toxin in a corresponding position into the opposite forearm. Schick control (heated and diluted diphtheria toxin) is supplied in 5-cc. rubber-diaphragm-capped containers.

The consensus of opinion is that all children, excepting those showing decided allergic tendencies, should be given the benefit of active immunization against diphtheria during the pre-school age (six months to six years) without a preliminary Schick test. The best means of accomplishing this is by the administration of not less than two, or not more than three 1 cc. doses of diphtheria toxoid (Ramon anatoxin) at intervals of three weeks.

Children of the school age and adults show more local and general

reactions to the bacterial protein of toxoid, so that an intradermal test for sensitiveness should be performed before administering the immunizing injections. If evidence of sensitiveness appears within three days after the intradermal test, the doses of toxoid should be altered and given as follows: 0.1, 0.25, 0.5, 1, and 1 cc. of diphtheria toxoid at intervals of one week instead of three weeks. The great susceptibility of the pre-school child justifies the elimination of the preliminary Schick test, but it is desirable to perform a preliminary test on older children, especially in urban communities where the opportunity is favorable for acquiring active immunity from exposure to attenuated infections. On the other hand, rural children show a greater susceptibility to diphtheria as indicated by more Schick positives than city children. This is because they are not as exposed as urban children, and consequently do not acquire immunity through exposure.

In the presence of what appears to be a case of diphtheria, the **isolation** of the patient is imperative under the same general measures as those described for the scarlet fever patient (Chap. 12, this volume). **Quarantine is not essential** since cultures of exposed persons are always taken, and if these are found to be negative and there are no symptoms of the disease, there is no necessity for detaining the subjects.

The indiscriminate protection of contacts by the administration of antitoxin, as was practiced for many years after its introduction, is no longer considered desirable. In institutions harboring a number of children, or in general hospitals where the facilities for separating contacts are limited, and where, owing to reduced resistance, the susceptibility of the contacts is greatly increased, the use of prophylactic injections of antitoxin may be justified. Otherwise, the use of antitoxin for passive immunization has many disadvantages and is by no means as effective as it was formerly thought to be. The protective value does not extend beyond three weeks; in fact, it has been known to last as short a time as eleven days. In view of this it must be borne in mind that the sensitization produced by the serum may result in anaphylaxis, which experience has shown may develop in those who have had an immunizing dose and later require a curative dose of the antitoxin owing to the subsequent development of diphtheria. Moreover, we have in the *Schick test* a method with which the susceptibility of those who have been exposed to the disease can with reasonable certainty be determined.

Separation and isolation of contacts, culturing the throat, and careful examination and inspection of the throat twice daily for the length of the incubation period, with the prompt administration of antitoxin at the slightest sign of trouble, are more advantageous than the indiscriminate use of antitoxin in the prophylactic treatment of contacts. If these measures are not feasible, passive immunization may be desirable, especially for those who give a positive Schick test.

The *immunizing dose* of antitoxin varies from 1000 to 1500 units, the larger dose being given to inmates of institutions or when exposure has been prolonged for five or six days. Infants from six to twelve months should have from 500 to 1000 units, while for those less than six months the dosage may be reduced, down to 100 units for the new-born child, should it be found desirable to immunize such young children.

The injection is given intramuscularly and is ordinarily not followed by any reaction, except perhaps a very little local discomfort, a tem-

porary rise of temperature and sometimes a transient urticarial, morbilliform or scarlatiniform rash.

Contacts, particularly young children, often appear to be suffering from a cold, which frequently proves to be diphtheria. Such a child should receive a curative dose and should be cultured and kept under observation.

The *curative dose* may be given intramuscularly or intravenously. The *subcutaneous method* has fallen into disuse owing to its slow absorption and to the greater and more prolonged discomfort attending the injections.

The *intramuscular* injection is simple, causing a minimum of discomfort; its action is, moreover, prompt and efficacious. The point of election is the anterior external surface of the thigh at the juncture of the upper and median thirds. The site, after being cleansed, is painted with **tincture of iodine**; the needle is then thrust well into the muscle, and unless the fluid is forced in with too great rapidity, little pain will be experienced. The wound should be closed with a small pledget of cotton and collodion.

In view of the fact that we are not in a position to determine with accuracy the virulence of a given attack, that is to say, the definite amount of toxemia with which we have to deal, the *dosage* will always, to a certain extent, be empirical, based largely upon experience. While in general large doses are desirable, certain factors enter into consideration. These are the general condition of the patient, his age, the duration of the disease, the location and extent of the diphtheritic process on the day the antitoxin is administered, the patient's susceptibility and the virulence of the organism. We have no way of dealing with the last two, so that they need no further consideration.

The effect of the toxemia on the particular individual must be considered in estimating the amount to be given. Two patients who have been attacked at the same time under the same conditions may present widely differing degrees of toxemia, the one showing marked pallor, listlessness, prostration, together with pronounced glandular enlargement and albuminuria, while the other is not nearly so severely affected. The former will, of course, require a larger dose than the latter. But the amount should never be reduced below a certain working minimum to meet the probable requirements of a given case.

The age of the patient is of importance only in that infants under two years of age should have about half the amount necessary for older children and adults. The dose should rarely, if ever, be less than 5000 units.

As to the duration of the disease, it is a matter of common experience that antitoxin given after the third day is much less efficacious and will require a larger dose than if given earlier. Therefore, in order to insure the best results in arresting the disease and the avoidance of complications and sequelae, the rule to be observed is *early administration and a sufficient dose at the first injection*. In general, it may be said that a larger dose than necessary does no harm, but an insufficient amount may result in the death of the patient. Usually one dose suffices to prevent the spread of the membrane; but if after from 12 to 24 hours the membrane appears to be extending and the general condition fails to improve, a *second* dose should be given.

Tonsillar cases in which the membrane is limited and the case is examined on the first day will require 10,000 units; if there is the least sign of dyspnea, 20,000 units must be given. A case examined on the second day of the disease should have at least 10,000 units, and after that 20,000 units or more should be given.

In nasal cases where there is but slight moisture from the nares and diagnosis is made by cultures only, the dosage, if administered on the first day of the disease, should be 10,000 units or more, according to the time that has elapsed from the onset of the disease and the institution of serum therapy. However, in nasal cases where there is a distinct membrane with discharge and signs of toxemia, 20,000 units should be given as an initial dose on the first day of the disease, increasing to 40,000 if seen as late as the third day.

The maximum total dosage that may be given to an individual during the course of the disease is limited only by the supply available for a single case rather than by any ill effects that may result from large doses. As much as 300,000 units have been given (subcutaneously), resulting in recovery.

With the proper technic carried out with antiseptic precautions and the use of a reliable sterile serum, complications do not occur from the use of antitoxin. Abscess formation at the site of injections is rare, especially if the intramuscular method is used, which avoids the marked and persistent soreness that follows the subcutaneous method.

Intravenous administration of antitoxin is particularly useful in the treatment of late, advanced cases. It has also been used with excellent results in moderately severe cases. It presents the great advantage of prompt action and of requiring a smaller dose than the other methods, and is therefore less expensive. Its prompt effect is readily explained when we consider that it is through the blood that the antitoxin is distributed to the place where it binds and neutralizes the toxins; it thus further prevents the toxin from passing out into the tissue cells. Park considers that 5000 units given intravenously are as effective as 20,000 given subcutaneously. Six hours after the injection the blood contains 20 units per cc. of blood as against 2 units per cc. of blood after subcutaneous administration of the serum. The membrane disappears more quickly; the patient feels well; the bacillus also disappears from the body sooner, and therefore the number of carriers is reduced; furthermore, fewer heart failures and fewer cases of paralysis follow during the course of the disease.

The injection can be made in the vein of the arm, but when this is not easily done, as in young children, where, owing to the smallness of the vein, it will often be necessary to cut down to it, the external jugular forms a convenient site for the injection. There is generally less pain during and after the administration of antitoxin by this method than by the other routes. Antitoxin of high potency should be used, say 2000 units per cc. and diluted about one-half with physiologic saline solution (the dilution being made in the laboratory), warmed to a little above body temperature and placed in an ordinary 5 or 10 cc. glass syringe at the time of making the injection; for children a No. 22, and for adults a No. 19, gage can be used. For ordinary cases, with membrane on both tonsils but not extending to the pillars, a dosage of 3000 units should suffice and need not be repeated; for more extensive involvement a single dose of 5000 should prove effective. In the more advanced and very desperate cases, 10,000 and even 20,000 units should be used. Sometimes in this type of patient it has been found advantageous to use both routes, that is, to reinforce the intravenous with the intramuscular injection of the serum.

Moreover, in spite of the fact that the subcutaneous injection of antitoxin has been almost entirely replaced by the intramuscular or intravenous route, Ramon and his associates, who reported their observations in an unusually virulent type of diphtheria in Europe, suggest that, in giving the single large initial dose generally advocated, one-half be given subcutaneously and the other half intramuscularly. In this way the more slowly utilized subcutaneous antitoxin serves to supplement the intramuscular antitoxin as it becomes less concentrated in the blood stream. The effect of the antitoxin is thereby prolonged over a greater period than if either route is used alone.

If a high potency serum is used very little reaction results from its administration intravenously; any reaction that does occur is but transitory and not worthy of consideration in view of the advantages the method presents. The only disadvantage is the delicate technic, which requires experience and skill.

A *serum reaction* from the injection of antitoxin results in a varying percentage of cases. The effect is manifested by an urticarial, morbilliform or scarlatiniform eruption accompanied by general malaise, fever, nausea, vomiting, violent itching, joint pains and sometimes edema. It is self-limited, requires no special treatment and is never serious. This reaction may appear as late as two weeks after the injection of serum.

Anaphylaxis, or serum sickness, on the other hand, is of moment in that it may lead to collapse and death. On the whole it is very rare, so that the urgent necessity of administering antitoxin entirely outweighs any danger that may be connected with its use. Indeed, in the face of a genuine Klebs-Löffler infection, we know of no contraindication to the use of antitoxin. Some persons who have been sensitized by a previous dose of the serum, and others suffering from what is known as horse asthma exhibit a tendency to develop serum sickness. A skin test is useful for detecting such individuals. The test is made either by scarifying the skin and applying a little serum or by injecting about 0.1 cc. of the serum intradermally. The appearance of an urticarial reaction in from 2 to 15 minutes indicates susceptibility. Such persons should be given serum treatment under special precautions and only after careful consideration as to which is the lesser of the two evils.

When the skin test indicates hypersensitiveness it is an indication that we may be confronted with a rather perplexing problem. We have to decide whether the danger of the serum reaction is equal to the diphtheritic infection. Fort contends that in most instances it is not. Park summarizes the consensus of opinion very nicely when he says, "I believe we are justified, without waiting for the result of an intracutaneous test, in giving an immediate intravenous injection in every severe case of diphtheria, unless we see evidences of status lymphaticus or obtain a history of asthma."

"The reaction from an intravenous injection is also not dangerous in the great majority of cases if the antitoxic globulin is given very slowly and is stopped at the first appearance of symptoms."

"Even after a larger dose of antitoxin, we need have no special fear of reinjecting antitoxin or serum."

"... the lesser sensitization given by toxin-antitoxin was in all probability a nearly negligible factor."

Coca, Walzer and Thommen quote Park in saying "that the inci-

dence of the positive cutaneous reaction varies greatly with sera from different horses. With one serum, for example, about sixty per cent of the individuals tested reacted positively, previous to the administration of the serum; with another serum, thirty-five per cent reacted, and with a third serum only ten per cent."

This observation is, of course, to be considered in connection with Park's earlier experience with Throne, namely, that the serum of some horses causes more general serum reactions (serum disease) than that of others.

These authors infer from the report of Park that even a marked skin sensitiveness to horse serum is not reliable evidence of a constitutional sensitiveness that would contraindicate the administration of therapeutic serum. The same authors contend that "the ordinary serum disease following a first administration of horse serum is rarely of such severity as to threaten the life of the patient, but the 'immediate' reaction following a repeated injection has actually caused death; and it is in this situation that the physician is apt to be most apprehensive and, as we shall see, most helpless. Fortunately, the frequency of the 'immediate' reaction is so inconsiderable that it seems proper to disregard the danger of it when the need for reinjection of serum appears urgent. On the other hand, such reinjection (after an interval of one week or more) should not be undertaken lightly."

They also remind us that the former procedure of desensitization by repeated subcutaneous injection of small doses of horse serum into horse-atopic persons would not induce an important increase in the tolerance to the serum within a few hours or even days. Moreover, when the fact is recalled that 0.05 cc. of horse serum is known to have caused death in a hypersensitive person and much smaller quantities have produced severe reactions upon intracutaneous injection, it is evident that the procedure of "desensitization" (or, better, hyposensitization) is wholly inapplicable when it is desired to administer therapeutic horse serum to an individual who is known, clinically or by the ophthalmic test, to be atopically sensitive to it.

From this then, in an unquestionable case of diphtheria, we have no choice but to give diphtheria antitoxin. It is well to have available a syringe loaded with from 0.06 to 1 cc. (1 to 15 minims) of a 1:1000 solution of epinephrine, diluted with sterile saline solution, to be administered in the event that immediate symptoms of reaction occur.

For *relapses* some caution is required in estimating the *dosage* of antitoxin. Although most authorities claim that these are apt to be milder than the original attack, and for that reason feel justified in hesitating to give the antitoxin unless the symptoms are alarming, the author considers that in the face of a genuine second attack of diphtheria a curative dose of antitoxin is in order, since it is the only certain cure at our disposal. It surely represents the minor of the two evils, since the risk of fatal anaphylaxis is so very much less than the effects of the disease, with death as a possibility. The discomfort from the reaction is in no way comparable to the comfort of feeling that a quick cure has been obtained. The author has never observed a fatal or even a serious reaction following a second or spaced injection of antitoxin in the large number of instances in which he has used it.

If every case of diphtheria could be examined during the first twenty-four hours after onset, the treatment could be summed up in two words

—**antitoxin, rest**—and the whole course of the disease from first to last could be described in three words, antitoxin, rest, recovery. But unfortunately this is too seldom the case, and the general management of diphtheria still requires consideration.

GENERAL MANAGEMENT.—For simple faucial diphtheria, if the patient is to be treated at home, the **sick room** should be **large, airy** and as **well ventilated** as possible, the **temperature** being kept at 65° F. (18.3° C.). Hospital patients should be allowed as many cubic feet of air as the circumstances permit. **Absolute rest in bed** is imperative even for the mildest cases, and for the severe ones it should be continued during convalescence. Owing to the danger of heart complications, absolute rest should be taken to mean the avoidance of all unnecessary movements on the part of the patient. At first no pillow should be allowed, but if this is too irksome one soft pillow may be permitted; at the slightest sign of heart failure it should be withdrawn, and, if necessary, the **foot of the bed elevated**. In mild cases the patient may gradually be allowed to sit up in bed, well supported by pillows during the third week, and to leave the bed for an hour or two at the beginning of the fourth week. The severe cases in which complications are to be expected should be kept flat in bed for at least five weeks, after which time, in the absence of cardiac or paralytic manifestations, a gradual relaxation of these strict measures may be allowed. But severe cases in which the much feared complications set in must be kept in bed for eight weeks or longer if the complications still persist.

The **diet** during the acute stage should be limited to **liquids—milk, beef juice, fresh fruit juice**—every three hours. **Overfeeding** should be avoided in order to prevent vomiting, the strain of which may react on the heart. Difficulty in feeding, which often arises owing to paralysis of the pharyngeal muscles, can be overcome by **nasal feeding** through a **catheter**. After the acute stage is passed, as shown by normal temperature, disappearance of local symptoms, and absence of renal involvement, the diet may be cautiously increased to include **stewed fruits, soft-boiled eggs, bread and butter, gelatin, light puddings, gruel, well-cooked cereals**, and can be rapidly followed by a full diet.

MEDICINAL TREATMENT.—There are no drugs that are in any sense specific for diphtheria. Stimulation of some kind is required in all cases during the acute stage. For the mild cases **strychnine** in moderate doses will suffice; the severer ones will require in addition **alcohol**, preferably **whiskey** or **brandy**, and also **caffeine**. During convalescence **general tonics** will be needed. Some form of **iron** is always indicated, preferably the **syrup of iodide of iron**.

It is important to keep the **bowels open** in order to avoid straining at stool, or vomiting, both of which may produce collapse owing to the weakened condition of the heart. For the same reason **purgatives** should be **avoided**.

We cannot afford to ignore the function of the kidneys in diphtheria. Although actual nephritis is rare, it is not unknown and must be guarded against by the usual measures for free elimination. In some severe cases of diphtheria with vomiting, the latter may be due to a previous acidosis. For this condition the administration of large doses of **alkali** daily every four hours, given at the earliest possible moment, is indicated.

The **management of laryngeal diphtheria** presents a more complex problem, inasmuch as in addition to the intoxication there is the me-

chanical obstruction to breathing with asphyxiation as a possibility. Sometimes breathing may be made a little easier by keeping the patient **warmer** than in the pharyngeal cases and by the use of **steam** from the **croup kettle** and allowing **free access of fresh air**. In using steam in the laryngeal cases care should be taken not to exclude the air. A simple canopy with the spout of the croup kettle so situated as to allow the steam to flow toward the patient's head will be sufficient. Often the patient will show evidence of the relief experienced in placing his head directly in the path of the current of steam. The addition of drugs (medicated vapors) such as **tinctura benzoini composita** to the steam gives no better results than ordinary steam. It may be added, however, as the odor is desirable to some patients.

For the treatment of **dyspnea**, **turpentine stupes** applied to the **neck** and **upper chest** have proved of great advantage. Relief is often prompt, and appreciation is often expressed by the older patients. For the stupes, the following may be used: **oleum terebinthinae**, 2 fl. dr. (7.5 cc.); **oleum olivae**, 1 fl. dr. (3.75 cc.), in hot water, 2 pts. (1 liter), mixing it in a two-quart (4-liter) container, from which it is poured into a basin as needed. A piece of **flannel** (about one-half yard) is wrung out of this solution, fluffed, tested as to heat, and then snugly **applied to the larynx and upper chest**, and changed frequently (every few minutes) so as to have the warmth applied continuously. As an emergency measure it will often be found useful to **rub the chest** thoroughly with **camphorated oil**, followed by the application of **hot flannels**. If hot water is not available the flannel can be heated around an electric light bulb, or other convenient sources of heat.

LOCAL TREATMENT.—In the treatment of diphtheria we have the tremendous advantage of possessing a specific which has a direct effect on the local process, so that local treatment is of no great importance. The antitoxin clears the exudate, while other measures are useful mainly in assisting in the separation and hastening the clearing away of particles of membrane, and for their general cleansing effect. All patients who can help themselves should be encouraged to keep the **mouth clean**. Dobell's solution or liquor antisepticus (U. S. P.), sodium perborate, and similar bland gargles or mouth washes will be found useful. Nasal drops of 10 per cent neosilvol or argyrol, ephedrine or adrenalin solutions are equally useful. The following mixture has also been widely used during the convalescent period:

℞	Mentholis	
	Acidi carbolici	āā Gr. ii (0.13 Gm.)
	Iodi	Gr. i (0.065 Gm.)
	Camphorae	Gr. iii (0.20 Gm.)
	Eucalyptol	fl. 5 ss (2.0 cc.)
	Liq. albolene	q.s. ad fl. 3 i (30 cc.)

M. Sig.: Five drops to be instilled into each nostril three or four times daily.

Those who resist this treatment, especially young children, had better be let alone on account of the danger of heart failure from undue exertion.

For *internal medication*, **ammonium carbonate** and **syrup of ipecac** are sometimes valuable in hastening the separation of the membrane in the laryngeal cases. But should these measures fail, operative interference—**intubation** or **tracheotomy**—must be resorted to.

SURGICAL TREATMENT.—The indications for operative interference are well-marked dyspnea with recession of the soft parts of the chest, restlessness, and a weak, rapid pulse, particularly if the symptoms have not yielded to serum and other treatment.

The proper *time* for interference is a matter of judgment gained only by experience. Operation should not be done too early, since manipulation and the possible damage to the soft parts, together with the presence of the tube which acts as a foreign body, may increase the dangers of an already serious condition, a risk which should be avoided whenever possible. On the other hand, if it is delayed too long, the patient may lose strength and be unable to recuperate in spite of the success of the operation.

Intubation is better suited for hospital practice, where trained attendants are always available, than for patients treated at home. However, in a private case in which operative interference is not urgently required, intubation is sometimes indicated in order to permit the doctor to leave his patient with a greater feeling of security. Especially is this so if not much harm can result before aid arrives, in case a tube is coughed up. In more serious cases tracheotomy is the choice for private practice.

Intubation.—For intubation the patient, in a recumbent position and with the hands down, is placed in a sheet which is securely fastened about him. With the neck and shoulders resting on a pillow or a rolled blanket, the head is thrown back and is held by an assistant standing at the head of the bed or table, who at the same time places the mouth-gag in position on the left side of the patient's mouth. The operator then very gently passes the left index finger along the tongue to its base until he feels the epiglottis, which he turns back. The finger then enters the larynx and rests upon its posterior wall, care being taken not to interfere with the proper intake of air. The operator then passes the tube back until its point comes in contact with the left index finger. With the finger as a guide, the end of the tube is then engaged in the larynx, the handle of the introducer is slightly raised and the tube allowed to drop in with very little pressure. The obturator is then disengaged and the tube firmly fixed in position. A string, or better still, a No. 4 banjo wire, is securely looped in the hole at the end of the tube and allowed to remain in place, being attached to the outside of the patient's cheek by means of adhesive plaster. The string or wire should be drawn fairly taut so as not to cause extubation by the tongue. When the intubation has been completed the foot of the bed should be elevated to facilitate drainage and thus lessen the possibility of pneumonia. In order to prevent the removal of the tube by the patient himself, his arms should be restrained by the application of light splints. The tube should be taken out in four or five days, especially if the temperature and respiration are normal.

Extubation.—Extubation is simple, provided the tube has been anchored according to the above method, much more simple than when the regular instrument or extubator is used. By drawing the string or wire taut with the fingers of the one hand and passing the index finger of the other hand along the string to the larynx, the tube can be lifted out in a few seconds with practically no disturbance to the patient. The child need not be taken out of bed; indeed, very often the removal can be made during sleep without his knowledge.

In removing the tube, the weather and the time of day should be taken into consideration. The early forenoon of a bright sunny day is the best time to choose, since respiratory difficulties are most apt to occur at night and in damp weather. Sometimes the patients do not do well after extubation and may require the use of steam as above indicated for the relief of dyspnea; but should actual dyspnea set in, reintubation may be demanded, the tube being again removed in four or five days.

Intubation, as already indicated, should be done only after other efforts have failed to give relief, for the reason that we wish to avoid unnecessary trauma to the soft parts. A tube in the larynx acts as a foreign body, causing increased secretion and retention, which in some instances leads to ulceration. If after the repeated removal of the tube the child is unable to do without it, he should be taken to a specialist after the quarantine has been removed. In the management of tube cases fresh air and a warm sunny room are of great importance.

Tracheotomy. The technic of tracheotomy for the relief of diphtheritic laryngeal stenosis is the same as for any other similar condition. The patient is wrapped in a blanket or sheet (as for intubation) and the head kept back by placing a rolled blanket, 4 to 5 in. (10 to 12.5 c.) in diameter under the neck and shoulders; the site of operation is prepared with **iodine**. Nitrous oxide is used as an anesthetic if available, and ether should be second choice. In emergency and in extreme cases the operation may be done without an anesthetic.

The operator, steadying the trachea with his left hand, locates the upper two or three rings of the trachea and makes a fairly free incision 4 to 5 cm. (1½ to 2 in.) long. He carefully divides the tissues in the median line (it is of the utmost importance that the incision be made in this line and that the knife does not deviate from it), and is followed up by his assistant, who keeps out of the field the thyroid gland and any vessel that may be present. As the trachea is reached the finger is placed in the wound and two or three rings are cut through with the knife. This is usually followed by violent coughing. The wound should be held open by dilators or by the handle of the knife held at right angles to the incision until the coughing ceases and breathing seems tranquil and easy. In the meantime a search can be made for particles of membrane, which are removed with forceps. The tube is now inserted and held in position by tape strings placed in the ends of the tube and fastened around the patient's neck. A simple dressing of sterile gauze is placed around the tube and over the wound and is protected from the secretions of the latter by a flap of rubber tissue. Should there be much mucus or hemorrhage the table, or the foot of the **bed**, can be **elevated** to facilitate drainage by gravity away from the trachea and the lungs.

It is sometimes necessary to operate quickly and to plunge right in without all these precautions. This presents no great difficulty provided the median line is kept. Any hemorrhage that results is venous and can be easily controlled.

The tube should not be disturbed as long as the breathing is not interfered with; but in case of any embarrassment to breathing, which may happen owing to the presence of mucus plugging up the tube, it will only be necessary to remove the inner tube and clean it out. Carbol, the vegetable digestant which acts on dead tissue, has proved to

be useful in facilitating the removal of mucus and membranous plugs from tubes. An intubated patient should be under constant care to prevent suffocation through the plugging of the tube. The dressing can be changed once or twice every 24 hours. The use of steam inhalations will not be necessary if the room is warm enough. Lacking this, the steam from the croup kettle, so placed as to allow the currents of air to carry the steam to the patient, will be sufficient to moisten the atmosphere and warm the room.

The most dreaded effect of tracheotomy is the development of bronchopneumonia; therefore, a return to normal temperature and respiration is a welcome sign, indicating that the danger is passed. But prognosis is not good if there is a profuse discharge of thick tenacious mucus.

After sufficient time has elapsed to permit the separation of the membrane—from 2 to 4 days—the patient's ability to do without the tube can be tested by plugging the opening. If no embarrassment to breathing results, the tube may be removed and the wound covered with a plain dressing of gauze. It may sometimes be necessary to keep the tube in for several weeks or even months. In the case of nervous children who are apt to imagine that they cannot do without the tube, the test can be made by using a dummy tube, that is, one large enough to fill the wound but not long enough to reach into the trachea.

TREATMENT OF COMPLICATIONS.—**Antitoxin**, if given in sufficient amounts and early in the disease, will prevent complications. But should they occur their treatment is the same as when these conditions arise from other causes.

Cardiac symptoms will require **rest**, as nearly absolute as possible, quiet, fresh air, the administration of **tonics** and **attention to bowels and diet**, as already mentioned. The value of stimulants is sometimes questioned, but **strychnine** is generally given in tonic doses. Cases that present such marked symptoms as syncope, vomiting or precordial pain may require, in addition to the strychnine, **alcohol**, **atropine**, or **camphorated oil** and **hypodermics of morphia** as a sedative. **External heat** and **raising the foot of the bed** may also be useful in allaying the alarming symptoms. If vomiting occurs the withdrawal of food for a period of 12 hours often proves helpful. Any medication during this period should be by hypodermic.

The *paralyses* of diphtheria, like heart failure, can usually be avoided by sufficient and early serum therapy. They are generally transient and will require little treatment except **rest**, **fresh air**, and perhaps the pushing of **strychnine** internally. **Physical therapy**, such as massage, may be helpful, but it should not be started too soon.

Where the paralysis affects the muscles of deglutition the **foot of the bed** should be **elevated** in order to prevent the saliva from collecting, since it may cause suffocation or aspiration pneumonia, the patient actually drowning in his own secretions. The mouth should be kept free by gently **soaking** up the collection of **saliva with gauze sponges**. **Feeding** in these cases is best accomplished **by means of the catheter through the nose**. The bed supports should, of course, be removed during the process.

Bronchopneumonia is treated by placing the patient in the **open air** and the use of **supportive measures** as indicated by the condition when due to other causes.

Nephritis in diphtheria is generally not so serious as in scarlet fever and as a rule yields readily to simple treatment—careful **diet**, free intake of **water**, **diuretics**; in short, all the measures recommended for scarlatinal nephritis, except the hot pack. This is rarely required, and indications for its use should be carefully considered on account of the risk of aggravating the heart condition by too active treatment.

Otitis, otorrhea and their sequelae are not the problem in diphtheria that they are in scarlet fever, but treatment is the same as that outlined for the latter. The discharge from the ear may be due to mixed, or even to nondiphtheritic, infection, but the patient should not be considered free from infection until after careful and exhaustive study of the discharge has been made as to its noninfectious character.

Adenitis, likewise, is not a serious complication of diphtheria. It can be treated by **ice-bags** during the first 24 to 48 hours after its onset, and if these are not effective in reducing the swelling, **heat** should be tried. Aggravated cases may require **operation** under the same precautions as indicated for interference in cervical adenitis in scarlet fever. Sometimes, however, the deeper glands are involved without involvement of the skin. Indications for surgery would then rest upon the general symptoms such as septic temperature, rapid pulse and the persistence of the swelling.

MANAGEMENT OF CONVALESCENCE.—Owing to the severe anemia and the depressing effects of the disease, the management of convalescence of the diphtheria patient is perhaps of greater importance than that for other conditions. The danger of late heart failure and the possible development of late paralysis must always be borne in mind. The patient should be kept in bed for at least two weeks after the throat has cleared, and longer if there are any signs of cardiac weakness. The heart action must be carefully watched. The slightest indication of trouble, especially a slow, full, irregular pulse, always demands complete **quiet** and **rest in bed**, in order to avoid the fatal syncope which always threatens in such cases.

After the patient has been pronounced ready for discharge, he should, if possible, **not resume the routine of active life for some weeks after recovery** in order to avoid possible late complications from overstrain on the affected muscles, as, for example, ciliary paralysis or strabismus from reading too much, or other late paralyses.

An annoying problem of diphtheria convalescence is the *carrier* in whom the organism persists in the recesses of the affected parts. This often delays the discharge of the patient when otherwise he is to all appearances cured. It is good practice not to pronounce a patient ready to return home until two or three successive cultures have been returned negative, taking into consideration, of course, the duration of illness and the condition of the local parts. The question of discharging patients varies also according to the local laws of health. The favorite sites for the lodgment and retention of the organisms are the tonsillar crypts, the nasopharyngeal adenoid tissue and the nasal sinuses. **Local anti-septic treatment** is sometimes advised but has never proved uniformly effective. In some instances in the case of these persistent carriers, the organism will be found upon inoculation tests to be avirulent, and the patient may be allowed to go home. **Change of air** and an **outdoor life**

may materially assist in ridding the body of the organism. But in the very stubborn cases the only really curative measure is the appropriate **operation for enlarged or diseased tonsils and adenoids**. Operation should, of course, be deferred until the patient has completely recovered or at least so far recovered as to render it safe.

Attempts at curing the bacillus carrier by "**overriding**," that is, by the use of sprays of other organisms and by intramuscular injections of milk, have been reported favorably from some sources, but their practical value has not been demonstrated.

Prognosis.—The importance of early administration of antitoxin in the prognosis of diphtheria has been referred to several times directly and indirectly in the course of this discussion. While treatment on the first day insures not only a mild course of the disease, with less risk of paralysis, but also recovery in practically all cases, the prognosis grows gradually less favorable with each day that elapses before the first administration of the serum, and becomes dark indeed if treatment is delayed beyond the fourth day.

Much of the prognosis of the disease, of course, depends upon the age of the patient and the previous condition, as well as upon the extent of the membrane, the rapidity with which it spreads and the particular type of the disease. Children under two years of age are more apt to develop laryngeal diphtheria, which is the most serious type of the disorder. On the whole, therefore, diphtheria in a child before the third year of life is more dangerous than later in childhood.

As to remote effects, although paralysis is sometimes persistent for a long time, permanent disability is rare, and the effect of the toxemia on the heart is not known to be of a permanent character.

Pathology.—The effect of the diphtheritic organism which finds lodgment in a minute breach on a mucous membrane is seen in the local deposit of a fibrinous exudate, the characteristic clinical feature of the disease. But pathologically the essential lesion is the degenerative and exudative change in the sinuses beneath the affected mucous membranes in which the main effects of the toxin are seen. The changes involve principally the epithelial cells of the mucous membrane concerned, the heart muscles, the lungs, the kidney, liver, spleen, the alimentary canal, the lymph nodes, the ductless glands, the central and peripheral nervous systems, the bone marrow and the blood.

The pseudomembrane is the result of degeneration, necrosis and desquamation of the epithelial cells followed by increasing exudation of fibrin and the gradual formation and increase in thickness of the membrane. Under the microscope the membrane is seen to consist of an interlaced network of fibrin in which are found degenerated epithelial cells and clumps of bacilli, the latter being best observed in the lower and newer layers. Sometimes there is also an admixture of pyogenic cocci, such as streptococcus and pneumococcus. In addition to the local formation of the membrane the bacilli are active in elaborating toxins which are carried by way of the lymphatics and the blood stream from the original point of attack to other locations, from which they continue to give off toxins. The disease, therefore, may also be general as well as local, although there is little doubt but that the "great poison factory" is at the original site of invasion. Destruction of the superficial layers

of the epithelial cells opens up avenues for the absorption of the toxins, and the more the local lesion is permitted to spread the more numerous will be the locations liberally supplied with lymphatics that will become affected, and the more pronounced the toxemia that results.

Heart.—The greatest interest in the pathology of diphtheria centers upon the changes in the heart muscle. Councilman, Mallory and Pearce in their study have found some degree of fatty degeneration of the muscular fibers in many of the cases. The degeneration is variable in extent, sometimes affecting the general myocardium and sometimes only special foci. Fatty degeneration is seen along with more advanced forms of degeneration which result in the complete destruction of the muscle. The simple fatty degeneration occurs in severe, short cases, while the prolonged severe cases present more extensive degeneration. The phenomenon is due to the action of the toxin, which clinically manifests itself by the impaired heart function.

Thrombosis may result from primary necrosis of the endocardium.

Lungs.—The lungs are not only very frequently affected by the diphtheria toxin, but at the same time present the most serious lesions met with in the disease. In fact, it is often pulmonary involvement rather than the diphtheria itself which leads to death. The lesions are present in the form of bronchopneumonia, with a fibrinous hemorrhagic, serous or even entirely cellular exudate. Actual lobar pneumonia is practically never found. Thrombi are occasionally noted in the larger vessels but not in the capillaries. The lymphatics are generally seen to be dilated, containing coagulated albumin, fibrin or cells. They are often found packed with cells and large cells resembling those seen in the air spaces.

Alimentary Canal.—The alimentary canal is rarely the site of pathologic changes in diphtheria. In some few cases the stomach presents a definite membrane, which is usually limited in extent, although it has been known to involve the entire gastric mucosa. Very few diphtheria bacilli were found in this membrane by Councilman, Mallory and Pearce, but they appeared abundantly in cultures.

The intestinal mucosa shows few changes except more or less thickening, and some enlargement of the lymph-gland nodules of the small intestine.

Liver.—The liver presents no gross changes characteristic of the disease; they are the same as those found in other acute infections. The liver is swollen, tense and more or less congested. Microscopically the most constant lesion seems to be the swelling of the cells with increased granulation, especially in the center of the lobules. Sometimes there is fatty degeneration consisting of actual necrosis.

Kidneys.—The changes in the kidneys vary from epithelial degeneration, acute interstitial changes, to a glomerular nephritis; hemorrhage and chronic interstitial lesions are rare. But there is no type of lesion that can be considered typical for diphtheria.

The epithelial degeneration occurs in the larger number of cases and is nearly always the main or the only lesion. It is present in varying degrees and consists of fatty degeneration, hyaline degeneration affecting mainly the convoluted tubules, and the presence of casts. The most constant change is seen in the glomeruli, consisting of a small amount of granular coagulum between the tuft and the wall.

While there seems to be a general agreement between the albuminuria

and the degree of degeneration, there is apparently no such correspondence between the character of the degeneration and the general infection with various organisms, such as streptococcus, *Staphylococcus aureus* and pneumococcus, all of which have been found variously associated with the diphtheria bacilli.

The acute interstitial renal changes are generally associated with the more prolonged cases. Interstitial nephritis is evidenced by infiltration of the interstitial tissue with plasma cells; the infiltration, although it involves all parts of the kidneys, is more pronounced in certain foci than in others. The epithelial degeneration varies in different cases. The kidneys are enlarged only in the more pronounced ones.

Pronounced glomerular nephritis is found in only a limited number of cases and generally in the older patients and the more prolonged cases. The first evidence of the change is seen in the increase in cells and proliferation of the endothelium lining the vessels, followed later on by hyaline cellular degeneration.

Spleen.—The most marked features in the spleen are the presence of large phagocytic, epithelial-like cells in the lymph nodules, and necrosis of the lymphoid cells. The spleen is firm but not distended, smooth, and not markedly enlarged. The lymph nodes are nearly always distinct and sometimes even prominent.

Nervous System.—The lesions in the nervous system are still the subject of much discussion. Nearly all investigators, however, agree that the changes consist in degeneration due to a toxic parenchymatous and interstitial neuritis, some claiming that the condition is purely peripheral, while others show that it may be central, involving the spinal cord. In the peripheral nerves there is usually degeneration of the medullary sheath, which breaks up into globules; the axis cylinders become involved and may rupture crosswise, leading to degeneration of the nerve fibers below them. The primitive sheath remains intact. Both the sensory and the motor nerves may be affected, but some of the fibers probably remain intact, and the resulting paralysis is then only partial. Baginsky and others have described changes in the anterior cornua of the spinal cord, consisting of atrophy of the ganglion cells, hemorrhage in the gray matter of the spinal cord, degenerative changes in the various peripheral nerves as well as in the anterior and posterior spinal roots, and foci of exudates in the posterior roots.

Involvement of the vessels may lead to emboli with secondary involvement of the nervous system.

There is as yet no agreement as to whether the central or the peripheral nervous system is primarily affected in diphtheritic paralysis, nor has the nature of the changes been sufficiently elucidated to identify them positively as due to lymphogenous infection of the central nervous system. Some investigators attribute the condition to an ascending neuritis along the peripheral nerve centers, as in rabies and tetanus. Others believe it to be due to a lymphogenous infection; while still others, notably Bolton and Bown, do not admit this mode of infection but regard any involvement of the nervous system as part of the general systemic infection carried by the blood stream. Walshe, in what appears to be the most recent study of the question, inclines to the theory of a twofold mechanism. The early and most characteristic paralytic manifestation, he ascribes to an ascending infection of the central

nervous system. The toxin elaborated in the membrane passes up to the medulla in the perineural lymph channel of the cranial nerves, innervating the tonsils and the fauces; but the initial and essential lesion is produced not by the passage of the toxin in the lymph channels, but by its action on the central nervous system, *i.e.*, on the nuclei and nerves involved. The late paralysis is due to the generalized systemic toxemia. Clinically, it resembles a multiple neuritis—its delayed onset appearing simultaneously in all the spinal nerves—and is more lasting in its course than the earlier paralytic symptoms. Walshe thus accounts for the phenomena of faucial and of wound diphtheria, the latter being strikingly illustrated by one of the cases cited, in which a physician, while performing tracheotomy on a diphtheritic patient, had his right thumb infected. The paralysis first localized in the affected member and then became generalized in the spinal nerves, the cranial nerves never having been affected in the slightest degree.

Muscular System.—The muscles also are subject to severe changes. The skeletal muscles show the same fatty degenerative phenomena as are found in the heart and the nervous system where these are involved, but they are perhaps not quite so marked.

Bone Marrow.—The changes in the bone marrow are not distinctive of diphtheria since it shows the same hyperplasia as that found in other infectious conditions. In experimental diphtheria there seems to be some increase in giant cells and leukocytes to a limited extent, together with nuclear changes in the latter. The red blood cells remain unaltered.

Glands.—Of the ductless glands the thymus was the only one in which Councilman and his associates found any changes. It shows degeneration of the lymphoid cells, generally within the larger cells with vesicular nuclei, most marked in the vicinity of the Hassall bodies.

Blood.—The presence of the toxin in the blood of diphtheria patients is generally acknowledged, while the Schick test demonstrates the presence also of antitoxin in the blood of certain individuals.

The blood picture in the cases of diphtheria that do not receive antitoxin corresponds to the severe anemia that attends such cases clinically. In the untreated cases the red blood cells show a reduction of as much as over two million, while of the treated cases only a few present a reduced red blood count, which is also not nearly so marked. The hemoglobin decreases correspondingly but recovers more slowly than the red blood cells.

Leukocytosis may or may not be present. According to some authors the leukocytosis, when present, is promptly affected by antitoxin, but only if it is administered during the first twenty-four hours of the disease; the lymphocytes, on the other hand, show an increase after the serum injections. Myelocytes are a bad prognostic sign, especially in the absence of leukocytosis. On the whole, however, the blood is not of much diagnostic value in diphtheria.

Historical Summary.—Diphtheria appears to be one of the various infectious epidemic diseases that was known to very early writers, judging from descriptions found in ancient writings of ulcerative processes in the throat and of a pseudomembranous deposit on the trachea. Aretæus, a contemporary of Galen, in the second century of this era depicted a disease which is highly suggestive of diphtheria. He spoke

of a disorder, more common among children than among adults, in which a thick, moist substance formed over the tonsils and which may be superficial and benign, or extensive, malignant and putrid, causing a disagreeable, fetid odor from the mouth. He believed the disease to have been imported from Egypt and Syria and therefore termed it *morbus aegypticus* or *morbus syriacus*. He also mentioned the difficulty in swallowing fluids, which were sometimes regurgitated through the nose, the husky voice, and suffocation, that often led to a rapidly fatal end.

During the fourth century Macrobius described an epidemic of a disease that prevailed in Rome and which to all appearances was diphtheritic in character. After that time little is found in literature concerning such a disorder until it is again mentioned as prevalent in epidemic form during the fifteenth and the following centuries. These epidemics seem to be concerned mainly with the laryngeal type of the disease. Severe outbreaks of this type are reported from Spain and from Italy during the sixteenth and the seventeenth centuries, the Spaniards calling it *garrotillo*, while to the Italians it became known as *gulae morbus*. During the eighteenth century the disease appeared in epidemic form in France (1736), as *angina trachéale*; in England (1748) it was described by Fothergill as "the sore throat with ulcers"; it was reported in Holland in 1745; in 1752 severe epidemics were reported in Switzerland and also in America.

In 1735 Douglas described a peculiar form of sore throat which appeared in certain New England towns and gradually spread westward to the Hudson River about two years later. Douglas' paper, entitled "An Eruptive Miliary Fever, with Anginosa Ulcuscuclosia," was translated into French and later quoted by Bretonneau. An epidemic in New York, also in 1752, is described by Father Middleton. In 1771 Bard, a physician of New York, published a pamphlet entitled "An Enquiry into the Nature, Cause and Cure of the Angina Suffocative or Sore Throat Distemper," in which he gives a clinical description of a disease which in its essential features suggests diphtheria. After this no accounts of the disease in this country seem to have appeared until the middle of the nineteenth century, when it prevailed in some parts of New York State, being especially malignant in Albany. According to Caldwell (cited by Löffler) Washington was seized with the malady at his home in Mount Vernon.

In 1809 an epidemic of sore throat is reported from Philadelphia, and again in 1831, but diphtheria as the cause of death does not appear in the health reports of that city until the year 1860.

From a monograph on a severe epidemic of sore throat published by F. V. Fitzgerald in 1856, it appears that the disease had by that time reached San Francisco and other towns in California.

But the most accurate description of diphtheria is that by Bretonneau (1826) in France, who based his study on epidemics that prevailed in that country from 1818 to 1826. He recognized the specific character of the malady, giving it the name *la diphtérie* (ἡ διφθέρεια, the skin or membrane). He also regarded the exudate as the only source of infection, and believed that the contagium spread not through the air but by a sort of inoculation from particles of the exudate coming in immediate contact with moist mucous membranes. Bretonneau also

bears the distinction of being the first to note that the association of croup and malignant angina was not accidental. Inasmuch as adults who were suffering from malignant angina were able to infect children who then presented typical croup, and that the deposits on the tonsils and the pharynx were the same in both the croup and the angina, he was convinced that the two were dependent on one and the same factor. This, together with observations of points of differentiation between the scarlatinal and the diphtheritic anginose membrane, led him to the further conclusion that although appearing in various forms, diphtheria was a distinct clinical entity.

Bretonneau's main deductions were subsequently confirmed by Trousseau (1828), except that the latter regarded the specific affection of the mucous membranes not as a purely local process, but as part of the course of a constitutional disorder. He therefore substituted the term *diphthérie* for *diphthérite*, a change which Bretonneau accepted because he found that the term *diphthérite* or diphtheritis was being used in a sense different from that intended by him. Trousseau's theory gained a number of adherents, but in the light of our present knowledge, it is, of course, altogether untenable. His work is valuable for the description he gives of the very malignant forms with their destructive processes in the pharyngeal region and the general toxic phenomena.

The question of diphtheria as a distinct clinical entity continued to be a source of controversy for several decades. Though upheld by a number of investigators, it was opposed by so eminent a pathologist as Virchow, who claimed that in croup the membrane is deposited on healthy mucosa, while in diphtheria the exudate develops not only on the surface of the mucosa, but extends into its substance, and that it is this membrane which undergoes interstitial necrosis from lack of nourishment owing to compression of the blood vessels.

It is interesting to note that the transmissibility of the disease as suggested by Bretonneau received ample confirmation by a number of observations. One of these concerns Herpin, a physician of Tours, France (1843). While he was cauterizing the throat of a diphtheria patient the child coughed up a particle of membrane which settled on the doctor's nose and which he was unable to remove at once. He developed a severe nasal diphtheria, accompanied later by severe paralysis, from which he finally died. An instance of wound diphtheria is reported by Paterson (1866). A farmer who had inserted his finger, on which there was an open wound, into the throat of his child who was suffering from diphtheria, in order to remove an obstruction which had caused a fit of coughing, developed a membranous deposit on the open wound which extended over the entire finger. General symptoms followed. The finger healed in a few weeks, but several weeks afterward the man developed severe paralysis of the lower, and later of the upper, extremities which persisted for four months. At no time were there any throat symptoms.

In spite of these involuntary inoculations in man, the experimental production of diphtheria had up to this time met with only negative results, although Bretonneau had succeeded in producing a typical false membrane in the trachea of dogs by injecting a mixture of cantharides and olive oil. On the supposition that croup was caused by the inspiration of acrid, irritating substances, other investigators had previously

introduced acids, alcohol and other caustic substances into the air passages of animals with the idea of producing a membrane. Delaford tried chlorine, corrosive sublimate, arsenic, sulphuric acid and ammonia. He found the last the most suitable for these experiments, and this substance was later employed by others, notably Oertel (1871), in their experiments. But Bretonneau recognized that the resemblance of the artificially produced membrane to the idiopathic one was more apparent than real, since they differed so entirely in their clinical behavior. This observation was subsequently confirmed by Lichtheim in 1883.

The introduction of bacteriology into the arena of medical research was destined to solve the question that had been so diligently pursued since Bretonneau's classic work first appeared.

Before the true causative agent of diphtheria was finally discovered, attempts had been made to establish a relationship between certain fungi and the diphtheritic membrane. In fact, as late as 1881 Talamon described in detail a fungus which he had constantly obtained from cultures, inoculations of which produced thick, false membrane in animals and birds, especially the pigeon. But the fallacy of this theory was demonstrated by Duclaux.

In 1868 Huerter, and also Oertel, found small, round, rod-shaped and corkscrew-like, motile bodies in the blood as well as in the membrane and lesions of diphtheria patients, to which they ascribed a certain etiologic relationship to the disease. Similar bodies were also subsequently observed by von Reeklinghausen, Waldeyer, Nassiloff, Klebs, Eberth, Heiberg and others.

Although these investigators probably had observed the specific organism, they failed to differentiate it from the other bacilli present, a distinction which belongs to Klebs of Zürich (1873). There is a general impression that Klebs' discovery was not made until 1883, but at a Congress held at Wiesbaden ten years before that date he had not only announced his discovery of the diphtheria bacillus, but had also succeeded in obtaining it in cultures. The requirements of Koch for the specificity of a micro-organism, *i.e.*, that it must be found constantly arranged in a characteristic manner in the parts involved, that it must be isolated and obtained in pure culture, and that by inoculation into animals the disease must be reproduced in the latter, had not yet been fulfilled. Investigations of the subject were studiously carried on following Klebs' announcement. In 1883 Klebs, at the Congress at Wiesbaden, gave an account of his most recent researches and described in great detail the organism he had isolated as the diphtheria bacillus. In the same year Huebner endeavored to satisfy Koch's third postulate by experimental work. He attempted to produce an artificial diphtheritic exudate in the bladder of the rabbit by mechanical means, and to induce a general disease in other animals by the inoculation of the membrane. Although the animals died from an acute infection with extensive lesions of the bladder, and the infection was transmissible to other animals by inoculation of particles of the mucous membrane of the bladder, the organisms—micrococci arranged in short rods or chains—were found only in the vessels. Huebner, not being able subsequently to demonstrate these same organisms in the vessels of the affected mucous membrane of human subjects dying of diphtheria, concluded that these

bacteria in the membranes were saprophytic and that the organism of diphtheria had not yet been found.

Löffler in 1884, however, satisfied all of Koch's postulates and, confirming Klebs' original discovery of the specific organism, succeeded in producing the disease in the pigeon and in the calf. With the discovery of the Klebs-Löffler bacillus as the causative agent of diphtheria and the new trend of bacteriology toward the study of infection and immunity, investigations were directed to the study of the specific toxin and of the disease and immunization against it.

Roux and Yersin (1889-1890) directed attention to the capacity of the diphtheria bacillus to produce a soluble poison and to the fact that this power could be increased or diminished by cultivation on suitable media. Von Behring and Ehrlich later successfully pointed out the possible estimate of the strength of the diphtheria toxin, and their work was then followed by the studies of numerous investigators with regard to the behavior of the toxin in solutions and its method of action upon the constitution.

Local treatment of diphtheria by means of antiseptics with a view to preventing the formation of the membrane was at this time receiving great attention, but the conclusion was soon reached that these were of little value. Von Behring, in the course of his therapeutic studies, was led to believe that the main object of treatment must be directed toward neutralizing the poison of the diphtheria organism. In 1890 Fraenkel and von Behring began work on artificial immunization against diphtheria. Fraenkel worked in the direction of obtaining immunization by means of injections of large amounts of broth cultures of the diphtheria bacillus heated to 65° C. (149° F.), while von Behring followed the lines indicated by experiments with chemical substances. He inoculated guinea-pigs with diphtheria cultures which he immediately followed with therapeutic efforts at minimizing the induced disease by injections of iodine trichloride solutions, repeated for three days after the original inoculation. The animals thus treated survived while the controls died. The surviving animals also exhibited a greater resistance to infection than normal animals, two of them withstanding injections of virulent diphtheritic bacilli which killed controls in 36 hours. Von Behring described this resistance as similar to "the acquisition of immunity in man after convalescence from many infective diseases."

Thus the foundation of the treatment of, and active immunization against, diphtheria was laid.

Subsequent studies by Theobald Smith, Bela Schick, William H. Park, and Abraham Zingher of the United States, Glenny, Allen, and Hopkins of Great Britain, and Ramon of France brought it to its present state of perfection. The benefit to mankind cannot be estimated. It is one of the most conspicuous victories of "man against death." It will endure for all time as one of the most perfect examples of the treatment of disease with a specific serum, and of its prevention with a specific immunizing antigen.

It remains only for the physician to use the serum immediately on the appearance of any suspicious sore throat to bring about the day when a death from diphtheria will be an extraordinary occurrence. Moreover, if every child were actively immunized in the pre-school age period, the almost complete eradication of diphtheria would be assured.

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CHAPTER VIII

ERYSIPELAS

By H. B. CUSHING, M.D., C.M.

Definition, p. 177—Etiology, p. 177—Predisposing causes, p. 177—Exciting cause, p. 178—Symptomatology, p. 178—Clinical history, p. 178—Diagnosis, p. 179—Complications and sequelæ, p. 180—Association with other diseases, p. 181—Clinical varieties, p. 181—Treatment, p. 182—Prophylaxis, p. 182—General management, p. 182—Local treatment, p. 183—Specific therapy, p. 183—Prognosis, p. 184—Pathology, p. 184—Historical summary, p. 185.

Definition.—Erysipelas is also called, locally, "the Rose" and "St. Anthony's Fire." It is a contagious disease, characterized by a peculiar inflammation of the skin or, more rarely, of the mucous membranes, with constitutional symptoms. It is due to a specific microörganism, the *Streptococcus erysipclatis*. The infective organism remains local, the general symptoms being due to absorption of toxins and not to septicemia.

Etiology.—Erysipelas is endemic in most communities. It is seldom seen in the epidemic form at the present time, and probably epidemics only occur from overcrowding, neglect of proper ventilation and aseptic precautions in hospitals.

Sporadic cases may occur at any time or place with no evident connection with one another. Probably many healthy persons act as carriers, the streptococci only being virulent under special circumstances of individual susceptibility and the presence of an entrance wound. Certainly, persons suffering from repeated recurrent attacks must perpetually carry the organism in their body.

PREDISPOSING CAUSES.—The predisposing causes are overcrowding and poor sanitation, also debility from chronic alcoholism or chronic wasting disease. Individual susceptibility apparently plays an important part. Wounds, slight traumatism or recent confinement also obviously predispose to the disease. Little importance can be placed upon age, infancy and old age being equally susceptible. The most frequent occurrence is between the ages of 35 and 55.

A variation in frequency according to season has been noted by some observers, there being an increased number of cases in the spring and fall months. Probably this is to be explained not by changes in the temperature or atmospheric conditions at these seasons, so much as by the habits of the population as to overcrowding and lack of open-air exercise.

EXCITING CAUSE.—The exciting cause is a streptococcus first described by Fehleisen as *Streptococcus erysipelatis*. It is apparently a special strain of the *Streptococcus pyogenes* and indistinguishable from it morphologically or by cultural peculiarities. It is readily found in the lymph-spaces at the spreading margin of the lesion and easily cultivated on ordinary culture media. It is easy to demonstrate the disease by inoculation of cultures into the ear of a rabbit, and it has often been produced in man by inoculation, this experiment being carried out for the cure of chronic skin diseases, such as rodent ulcer or sarcoma.

In ordinary cases the streptococci remain localized in the skin lesion, but in exceptional cases they may be cultivated from the blood or found in the various organs of the body. The organism is probably conveyed from one patient to another, by contact infection, especially by means of the hands of attendants. It gains access to the body through some wound or abrasion, which may be so slight as to escape notice, or may heal during the incubation period of the erysipelas. The fact that the disease on the face usually starts at the margin of skin and mucous membranes, where excoriations are frequent, supports this view.

Symptomatology.—**CLINICAL HISTORY.**—*Period of Incubation.*—The incubation period is short, 2 to 8 days, most commonly 3, and is characterized by no symptoms. When the disease is experimentally produced in man, as has been done for the treatment of incurable tumors, the incubation period is 15 to 61 hours.

Mode of Onset.—The onset is abrupt with a sharp rise of temperature. There is usually a chill, often as severe as in the onset of pneumonia. Occasionally, in children, the onset is with a convulsion. Vomiting frequently occurs, but not always. The local lesion is usually to be noted simultaneously with or very shortly before the general symptoms.

Course.—The symptoms of the disease fall naturally into two groups: (1) those due to the local lesion, and (2) the constitutional symptoms.

(1) *Local Symptoms.*—The local lesion in 90 per cent. of the cases is situated on the face, beginning usually at the nostril or bridge of the nose, occasionally on the lip or external auditory meatus. The next most common site is in the leg, in about 8 per cent. of the cases, usually starting from some abrasion or sore, but the disease may also start in any wound or abrasion of any part of the body. A sharply defined patch of redness appears on the skin. This is raised, hot, swollen and shiny, and accompanied by a feeling of burning or tension. It gradually spreads by direct continuity to surrounding areas. The margin of the patch is most characteristic. It is raised, palpable, usually irregular in outline. It progresses steadily, and its gradual advance may be noted from hour to hour. The surface of the area involved is usually smooth and shiny, occasionally marked by small vesicles or blebs containing clear fluid. As the margin advances, the original area becomes gradually less swollen and the redness fades. The inflammation lasts in a particular spot for three or four days so that the disease may still be spreading in other parts when the original focus has become normal. When the

disease spreads over loose tissues, there is great edema of the parts. The eyelids, in particular, become so swollen that the eyes are closed; the ears may become greatly thickened, and at times the natural wrinkles of the face may become obliterated. As the inflammation subsides, the skin is left somewhat discolored and usually desquamates either in branny scales, or more rarely in sheets. The vesicles or blebs soon break and dry up, leaving adherent crusts. They occasionally become purulent and may leave shallow ulcers, sometimes causing a superficial gangrene. The nearest lymphatic glands are almost invariably enlarged and tender.

The inflammation may attack the various mucous membranes either primarily or by extension from the skin, causing the same redness and swelling of the surface, but the appearance is not so characteristic. The nose is frequently entirely occluded, resembling an attack of acute coryza; the tongue may be extremely swollen, filling up the mouth; and the throat also may be attacked, causing edema and swelling of the soft palate and uvula. In exceptional cases, the disease may extend to the larynx, when one is apt to have rapid and fatal edema of the glottis. When the scalp is attacked, redness is not seen, but the area involved may be outlined by the marked swelling and edema. There is usually greatly increased pain and headache in these cases.

(2) *Constitutional Symptoms*.—Fever is the most noticeable and characteristic symptom. It is usually fairly high and continuous the first three or four days, becoming then more intermittent. It most often terminates abruptly by crisis, but this is rarely as abrupt and defined as in pneumonia, and frequently takes the form of a rapid lysis, for a period of two or three days. Occasionally, the fever is intermittent or septic from the first on, in some cases, the fever is low and may even be entirely absent. Delirium is common and there is often severe headache and anorexia; but, as a rule, the subjective symptoms of the fever are less marked than one would anticipate from the height of the temperature. Cases of so-called "wandering erysipelas" give an irregular fever lasting several weeks, an increase of fever usually being associated with a fresh local outbreak. The pulse is rapid, respiration slightly increased, the skin usually hot and dry, although in many cases sweating is coincident with the remissions of temperature. The urine is diminished and febrile in character, and a febrile albuminuria is almost constant. The spleen may be enlarged in severe cases. There is often present a functional cardiac murmur. Leukocytosis is practically constant and may reach a high degree.

Diagnosis.—There is no difficulty in diagnosing the ordinary case of facial erysipelas. The characteristic appearance of the local eruption, especially of the sharply-defined, raised, advancing margin, the presence of vesicles on the surface and the inflammation of the neighboring lymph-glands, are usually quite distinctive. The combination of this lesion with the sudden onset of constitutional symptoms and high fever forms a picture unlike any other disease with which we have to deal.

Cases of erysipelas without fever frequently occur, especially in recurrent attacks and in persons suffering from some other debilitating

disease. The character of the local lesion, however, remains unchanged and should readily establish the diagnosis.

Erysipelas of the mucous membranes of the nose or throat presents exceptional difficulties; an acute spreading inflammation associated with severe constitutional symptoms might arouse suspicion, but the diagnosis is rarely established until the characteristic involvement of the skin occurs.

DIFFERENTIAL DIAGNOSIS.—A *diffuse cellulitis* causes the most frequent difficulty, or the inflammatory edema extending from a *carbuncle*, a local *anthrax* or a *furuncle* in the nose. In all these cases there is more brawny induration, absence of the characteristic, ridge-like margin and of the definite constitutional symptoms. Again, erysipelas tends to heal in the center and spread peripherally, which eventually clears up the diagnosis.

Herpes of the face, especially *herpes frontalis*, may cause confusion for a time, but the sharp limitation to an area supplied by a branch of the trigeminal nerve and the differences in the character of the lesion soon clear up the question.

Acute eczema and *dermatitis*, e.g., that caused by primula poisoning, has occasionally caused mistakes, but the absence of constitutional symptoms and the fact that these diseases spread by the coalescence of small pinpoint lesions and never present a distinct raised margin, should obviate the difficulty.

Complications and Sequelæ.—*Abscess* formation is by far the most common and important of the complications, occurring in nearly 10 per cent. of all cases. The abscesses are sometimes superficial, arising from suppurative of the vesicles or blebs which are so common in the disease, and sometimes are more deep-seated, as in the subcutaneous tissues. Certain types of the disease and certain outbreaks or epidemics appear particularly liable to be associated with abscess formation.

Sometimes the inflammation leads to *superficial gangrene* or sloughing, especially over the ears, the tip of the nose, the ends of the toes and fingers. If the erysipelatous inflammation extends over the sacral region, it is almost certain to cause a *bedsore*.

Although the streptococci usually remain local in the lymphatics of the skin, they occasionally give rise to a *septicemia* or *pyemia*, and, as a result, abscesses in various organs, pericarditis, empyema and some of the most malignant cases of ulcerative endocarditis occur.

Again, the inflammation may spread locally, causing suppurative adenitis, suppurative arthritis, otitis media, mastoiditis and purulent meningitis. Periostitis, especially of the skull, has been noted in a number of instances.

The extension inward to the mouth and throat occasionally gives rise to edema of the larynx, bronchitis and pneumonia. Pneumonia may also arise from pyemia or from hypostatic congestion as in any severe fever—it is often streptococcal in origin, but sometimes due to other organisms.

Albuminuria is almost constant during the febrile stage and occasionally a true, acute nephritis occurs.

Relapse is not uncommon, especially slight flare-ups of fever with local extension of the disease, after it has been apparently arrested, and there is often noted a tendency to recurrence of the disease after a few weeks or months of immunity. These recurrences are apparently due to persistence of the streptococci in the tissues; they always occur in the same site, and are especially common if some pathological lesion, such as a chronic sinus, persists.

Repeated attacks may leave a thickened, unsightly condition of the skin, a sort of chronic edema, closely resembling elephantiasis.

Involvement of scalp usually leads to alopecia, but the hair grows in again after a short time, unless the attacks are repeated.

Chronic skin diseases, such as lupus, eczema, rodent ulcer and sarcoma, are often benefited and even cured by an attack of erysipelas, and some have gone so far as to inoculate the disease for the cure of such conditions, but this is not considered justifiable.

Association with Other Diseases.—Erysipelas in the past was always associated with wounds and operations, becoming epidemic in hospitals, and it was regarded as one of the dangerous complications which might follow any operation. Since the days of antisepsis, this association has become rarer until such a complication is practically unknown, though surgeons have a wholesome fear of the disease because of its past reputation.

It is still seen, however, complicating infected wounds and particularly arising from such lesions as ulcerating cancer, chronic sinuses or even ulcerating hemorrhoids.

Similarly, aseptic methods have banished it from modern maternity hospitals, but careless midwifery occasionally still leads to the almost uniformly fatal form affecting parturient women, and the equally fatal infection of the umbilicus in new-born infants.

Cachectic states seem to predispose to the disease, and it is not uncommonly seen in the very aged, and in persons suffering from chronic alcoholism. Needless to say, it is such cases which increase the mortality rates in hospitals. In such cases it usually arises idiopathically, i.e., there is no history of exposure to other cases of erysipelas.

Clinical Varieties.—Erysipelas is an unusually variable disease, and a number of distinct types are described, though all are due to the same infective agent.

MIGRATORY ERYSIPELAS.—Migratory erysipelas begins like an ordinary attack, but instead of terminating in the usual time, lasts for several weeks, the eruption gradually spreading to all parts of the body, and even recurring in some localities. This form is commoner in young children, and usually ends favorably in spite of the weakness and prostration from the long-continued fever.

SURGICAL ERYSIPELAS.—This form of erysipelas, originating from a wound, is fortunately rarer in these days of asepsis; it is still occasionally seen in the case of operations on infected areas, e.g., after mastoid

operations or operations on chronic osteomyelitis. It is worth remembering that the first appearance of the erysipelatous rash may arise several centimeters distant from the wound or point of entrance.

RECURRENT ERYSIPELAS.—Recurrent erysipelas is not uncommon, especially in cases where there is a chronic discharging sinus or infective lesion in the air cavities of the skull. The recurrences take place, as a rule, every few months and always affect the same area. The constitutional symptoms become less with each attack until they may be absent altogether.

ERYSIPELAS OF THE NAVEL.—This condition occurs in new-born infants where proper aseptic precautions have not been taken with the cord and is almost uniformly fatal.

AFEBRILE ERYSIPELAS.—This form is frequently seen in aged or debilitated persons, or in those suffering from some chronic disease, such as diabetes or nephritis. The prognosis is very grave except in the afebrile cases due to recurrent attacks.

CELLULOCLUTANEOUS ERYSIPELAS.—This title is given to a type of the disease tending to involve the deeper tissues and cause abscess formation. This type is apparently due to a special strain of organism and is characteristic of certain epidemics.

Treatment.—**PROPHYLAXIS.**—Erysipelas is a contagious disease, conveyed by contact infection. It may be carried by the hands of a third person, as, for example, a nurse or doctor. The patient, therefore, should be **isolated** during the attack and the ordinary precautions of disinfection taken, especially the frequent **sterilization** of the hands of the attendants. With the most ordinary precautions there is little danger of infection, even if a patient is treated in an ordinary general hospital.

In the past, fatal epidemics in crowded and unsanitary hospitals, where aseptic precautions were not carried out, have given an unduly bad reputation to the disease. However, cases of erysipelas should never be treated in the vicinity of surgical or maternity cases or by those in attendance on such cases.

The infection does not appear to be a persistent one, in connection with rooms or clothing. Thorough cleansing gives sufficient disinfection. In the case of the patient, the organism may persist a long time, especially if any chronic lesion, such as a persistent sinus or nasal discharge, is left. The period of isolation is usually determined by the healing of the local lesion.

GENERAL MANAGEMENT.—The general management is that of any acute febrile disease necessitating absolute **rest in bed**, abundance of **fresh air**, a **light but nutritious diet** with an increased amount of **fluid**. The bowels require attention by **enemas** or repeated mild **purgatives**, and the skin should be kept active by regular **sponge baths**.

The fever is apt to be high, but as the course of the disease is short and toxemia not usually marked, it rarely requires special attention. If there is much toxemia and delirium with high fever, **hydrotherapy** gives the quickest and most efficient relief. This is best administered in the form of the cold pack, cold sponging or an alcohol rub, though a

regular cold bath may be used in severe cases. If there is continued delirium, and want of sleep, it is better to use an occasional dose of **morphin**. If no cardiac weakness is present, a dose of **veronal** and **phenacetin**, each 5 grains (0.324 gram), will often secure a night's rest.

In cases of severe prostration or threatened cardiac failure, **stimulants** may be employed, but, unfortunately, are as ineffectual as in other acute febrile diseases. **Alcohol** should always be given to those who are accustomed to its regular use; **strychnin**, **caffein** and **digitalis** have also been advised to tide over the patient until the crisis occurs.

LOCAL TREATMENT.—Local applications have been advised in great profusion. Except for the relief of local distress, the feeling of tension, burning or itching, it is doubtful if they have any effect on the outcome of the disease. Probably **cold compresses** of either **ice-water** or evaporating **lead lotion** give the most relief. Tucker advises the use of a saturated solution of **magnesium sulphate**. Some patients get more relief from the use of a soothing ointment, such as **carbulated vaselin**, **zinc ointment** or an ointment containing **bismuth salicylate** or **calamin**. All these are best applied by means of a **mask**, or **dressings of lint**. For many years **ichthyol** in 20 per cent. to 50 per cent. solution or ointment had a great vogue, but it does not appear to give more relief than other applications of more agreeable odor and appearance. The application over the lesion of strong antiseptic solutions such as **iodin**, **carbolic acid** or **corrosive sublimate** cannot be too strongly condemned, as increasing the distress and risk of the patient without shortening the course of the disease.

Erysipelas is a local infection, spreading peripherally through the lymphatics of the skin, and it is quite possible to arrest its progress in selected cases and bring about an early abortion of the disease by establishing a barrier in advance of the lesion. The method should only be used when the medical attendant is prepared to give personal supervision to the case and see that an effective barrier of aseptic inflammation or compression is produced, entirely surrounding the lesion. This is best done by painting on a band of **liniment of iodin** one-half to an inch wide, about an inch in advance of the lesion and entirely surrounding it. This should be repeated in 12 hours and any sign of breaking through controlled by a fresh barrier farther out. A strong solution of **silver nitrate** has been used for the same effect. Others have advised the use of a strip of nonflexible **collodion** applied in the same way and painted on repeatedly so as to produce a trough-like depression with compression of the lymphatics. The method is innocuous, and well worth trying where the lesion is small and can be entirely surrounded.

SPECIFIC THERAPY.—Hamilton Bell, in 1851, advised the use of **tr. ferri perchloridi** in large doses, 1 to 2 drams (3.75 to 7.50 c.c.) a day, for the treatment of erysipelas, and for sixty years the use was continued. No explanation was ever given of its supposed action and the best authorities unanimously condemn it as irrational and apt to irritate the digestive system of the patient. **Quinin** in doses of 20 to 30 grains (1.3 to 2.0 grams) per day has also been widely used with as little justification

or beneficial effect. **Collargol injections** have also been advised as in septicemia, but there is little evidence in favor of the treatment.

The use of **streptococcus vaccines** in large and repeated doses, 100 to 500 million, repeated every day or second day, also has its advocates. It may be of value in protracted cases and probably has some effect in preventing recurrences in patients unusually susceptible to the disease.

The administration of **antistreptococcic serum** seems to offer more hope and is strongly advised by some authorities. It should be given in large doses and frequently repeated. Some cases appear immediately arrested and others not affected at all by the treatment. Possibly a variation in the strain of the organism may have something to do with the effect. A polyvalent serum should be used.

Prognosis.—Erysipelas in the sporadic form, as seen in ordinary practice at the present time, is an almost benign disease. Although the high fever, delirium and repulsive disfigurement would incline one not accustomed to the disease to a grave prognosis, the fact is worth remembering that, in the absence of other disease or complicating condition, the outlook is entirely favorable. The total mortality at first might incline one to doubt this optimism, as it varies from 5 to 10 per cent. in different series of cases. A closer investigation of the fatal cases, however, shows that they are almost entirely comprised of certain types of the disease. Erysipelas of the new-born is almost uniformly fatal. Wound erysipelas, as seen in the epidemic form in former war hospitals, was an appallingly fatal disease, and accidental erysipelas infecting wounds is still a serious affection. The form occurring in cachexias, as in cancer, chronic nephritis, senility, etc., also swells the mortality lists. The cellulocutaneous form with abscess formation gives a higher percentage of deaths. On the other hand, recurrent attacks are progressively less serious, and finally cause little constitutional disturbance.

Even the migratory form, where the fever lasts for weeks and the whole body is involved, usually resolves eventually without bad effects. It is surprising how much of the skin of the body may be inflamed, such an extent of surface as would be uniformly fatal in burns and scalds, and yet the patients do very well.

Unfavorable symptoms are the tendency to abscess formation or gangrene, and evidence of serious involvement of the heart or lungs. As a general rule, an afebrile course shows a lack of reaction on the part of the patient, and, with the exception of a few very mild or recurrent cases of erysipelas, most cases without fever end fatally.

An attack of erysipelas usually leads to complete recovery, no residue or defect being left. Occasionally, however, especially in repeated attacks, there remains a chronic thickening of the skin or lymphatic edema, which may cause disfigurement or disability closely resembling elephantiasis; happily this condition is rare. Permanent effects may also be left in exceptional cases in the form of endocarditis or chronic nephritis.

Pathology.—In the cadaver, the redness of the lesion disappears and there is left only a slight edema. Microscopically, the condition is

one of edematous dermatitis, with little fibrinous exudate and only moderate infiltration with leukocytes. There is infiltration of the cutis and subcutaneous tissues with serous fluid containing only a small amount of fibrin. The layers of the epidermis frequently become separated by serum-forming vesicles. Toward the margin of the lesion, the streptococci are found in great numbers in the lymphatic spaces, in the channels at the base of the papillæ, and in the crevices of the derma.

The internal organs in an ordinary case show only the changes associated with an ordinary sepsis, i.e., cloudy or hyaline degeneration.

In cases with secondary infection, one may find evidences of pyemia, malignant endocarditis and septic infarcts in the organs. As noted elsewhere, suppurative inflammation of the various serous membranes may occur, meningitis, pericarditis, empyema or arthritis.

Nephritis, if found, is usually of a degenerative type, or an exacerbation of a chronic nephritis. Occasionally acute septic nephritis may be seen.

Historical Summary.—Erysipelas has been recognized for centuries, but was formerly confused with acute eczema and all diffuse phlegmonous inflammations. Its contagious nature was first recognized about 1850 by English writers. Later Velpeau, in France, and Wernher (1862) and Volkmann (1869), in Germany, emphasized the same fact.

The specific organism was first described by Fehleisen of Berlin in 1883, and later experimental researches confirmed his findings.

The recognition of the contagious character of the disease and its tendency to cause outbreaks in surgical and maternity wards has led to its exclusion from most general hospitals, while most contagious hospitals make no provision for its care. As the infection is not ordinarily virulent, and easily controlled by simple precautions in nursing, there seems no reason why it should not be treated in separate rooms of an ordinary hospital, as typhoid, tuberculosis, syphilis and similar diseases are treated.

CHAPTER IX

VARIOLA (*Small-pox*)

BY SAMUEL SIDNEY WOODY, M.D.

Definition, p. 187—Etiology, p. 187—Predisposing causes, p. 187—Exciting cause: the organism, p. 188—Modes of conveyance, p. 189—Symptomatology, p. 189—Clinical history, p. 189—Diagnosis, p. 193—Complications, p. 197—Clinical varieties, p. 197—Treatment, p. 200—Prophylaxis, p. 200—General treatment, p. 202—Serum therapy, p. 206—Prognosis, p. 207—Pathology, p. 207—Historical summary, p. 209.

Definition.—Variola, or small-pox, is a highly communicable, acute, specific infection characterized by a rather constant incubation period, sudden onset with high initial fever and marked constitutional disturbances lasting three to four days, followed by an eruption which begins as papules and passes into vesicles, pustules and crusts; and by a secondary rise of temperature during the pustular stage of the eruption.

Etiology.—PREDISPOSING CAUSES. —*Climate.* Before the introduction of vaccination, small-pox was one of the most prevalent and destructive scourges with which mankind was afflicted, destroying countless lives every year. There is no part of the world in which variola is not known, so that it cannot be said to be influenced by climatic conditions.

Season.—Seasonal influences are apparent in the fact that it is more prevalent in cold weather and that epidemics that break out in the spring and summer months are apt to be less extensive than those that appear in winter.

Age and Sex.—All human beings, irrespective of age or sex, are susceptible to the disease. Infants do not exhibit the natural immunity that they generally show toward infectious diseases. They are known to have been infected *in utero*, but only when the mother herself has had the disease during pregnancy, and may at birth present the rash or sears of the rash. As a rule, however, the fetus is not affected and a child born in a small-pox hospital, if vaccinated at once, may escape the disease.

Race.—As to race, there seems to be a general impression that colored people are more susceptible than are white people. This would apparently be substantiated by the fact that negroes are decidedly in the majority among the variola patients of a hospital for contagious diseases. But on second consideration it is more likely to be due to social and educational conditions, inasmuch as small-pox generally

arises among the poorer classes, where the evils of over-crowding are active, especially more so during the winter than during the summer when the windows are kept open and the people spend more of their time in the open air: and, secondly, there is the fact that vaccination is not so generally practiced among this class.

EXCITING CAUSE: THE ORGANISM.—Early studies sought to find the exciting cause of variola among the bacteria, but inasmuch as it was subsequently shown that the contents of the vesicle and the vaccinal lymph when deprived of their bacteria still retained their specific characteristics, this theory could not be upheld. Later investigations demonstrated the cause of variola to be an animal organism. Van der Loeff, and Pfeiffer, independently and almost simultaneously, in 1887, described the parasites, rhizopoda and sporozoa, which they found in the vaccinal lymph and in the contents of the variolous pustules, and to which they assigned an important rôle in the etiology of vaccinia and variola. But Guarnieri, in 1892, was the first to advance a definite protozoan theory in relation to vaccinal variolous infection. He demonstrated that the two diseases owed their specific character to the endocellular action of minute protozoa which he designated respectively, *Cytorrhcytes variola* and *Cytorrhcytes vaccinia*. Other investigators thereupon demonstrated that the parasite in certain stages assumed ultramicroscopical proportions, and further studies were then directed to establishing the morphology and structure of the organism. In 1904, Councilman and his associates demonstrated that these vaccine bodies were a phase of the development of a sporozoön. They definitely regard them as the cause of the disease, resting their assumption on the fact that they are always associated with its lesions, that they develop as it develops and are found under no other conditions; and that after the lesions have reached their full development, i.e., after local immunity is established and the cells are no longer capable of affording a suitable place for development, the organisms are no longer found. They also believed that variola and vaccinia are due to the same organism, in vaccinia cytoplasmic forms alone being met with; but in the calf and in the rabbit the organism occurs with the same regularity, whether the material used is that from vaccinia or from small-pox.

Prowazek and his followers (1907-1911) describe minute organisms as the etiological agents in variola and vaccinia, which they place among a group of protozoa termed by Prowazek as *chlamydozoa*, the life history of which is as follows: (1) Numerous elements intracellular as well as extracellular, which are filterable and which are present at the beginning and end of infection; (2) intracellular initial bodies; (3) transition stages to Guarnieri bodies with central inclusions and peripheral zone and accessory bodies; (4) various stages and forms of Guarnieri bodies, some of which, with their inclusion bodies, are also found on the peripheral zones; (5) finally, degenerated Guarnieri bodies and initial intracellular bodies which again break up into innumerable elementary bodies.

More recently Hallenberger reports results which somewhat modify

the findings of these observers. He points out that the difference between the extracellular and the intracellular bodies is developmental, the former increasing by simple division and the latter by budding. He terms the bodies he observed *strongyloplasma*, and places them between bacteria and protozoa, the Guarnieri bodies being reaction products of the cells. The fact that these are so numerous in the experimental lesion in the cornea of the rabbit and less frequent in the products of human poeks led him to abandon the term chlamydozoa and substitute the above-named for it.

Modes of Conveyance.—Infection of variola is carried from man to man, generally occurring through contact with the contents of the efflorescences, or the local lesions, in which the contagium resides. The virus of variola is peculiarly tenacious, so that contagion may also take place by fomites, especially through infected clothing and, according to some authorities, by aërial convection, and also through insects. Variola is contagious at all stages of development from the incubation through to the last stage, indeed, until the last evidence of crusts or "cores" has been removed from the hands and feet. In fatal cases it persists after death, thus making the most careful handling of the body a matter of supreme importance.

The secretions and excretions of the body play a subordinate rôle in the transmission of the disease. They are of importance only if infected through contact with the sores on mucous membranes or with the pustules. From tests made with the blood it seems that the blood of variola patients contains the activating agent only in the early stages of the disease—before the eruption develops.

Second attacks may occur, a few being recorded. But many of them are errors in diagnosis, for experience in hospitals—especially during epidemics—shows that all manner of diseases are liable to be sent in with a diagnosis of variola.

Symptomatology.—CLINICAL HISTORY.—*Period of Incubation.*—The incubation period of variola is generally considered to run from ten to thirteen days after a known exposure. It may be as short as five days; or it may be prolonged to the fourteenth or fifteenth day. The period of incubation is generally symptomless.

Mode of Onset.—The transition to the actual invasion of the disease is apt to be sudden, the symptoms consisting of headache, severe backache, fever, chilliness, stupor and delirium, with evidence of marked toxemia. The initial symptoms, however, may be very slight, and are then apt to be followed by a mild form of the disease, but it cannot be said that severe initial symptoms necessarily indicate a subsequent severe course of the disease.

The onset is generally so acute that the patient is at once prostrated and unable to be out of bed. The temperature, whether or not preceded by a chill, mounts rapidly to 103.1°-104° F. (39.5°-40° C.), and on the second or third day reaches a maximum of 104.9°-105.8° F. (40.5°-41° C.) and even 107.6° F. (42° C.). This rapid rise in temperature is often seen also in varioloid, while in the more severe forms of variola

lower temperatures are sometimes noted. The pulse, ranging between 108 and 120, is generally of good quality, except in the very severe cases, where it is apt to be thin and irregular. Respiration corresponds to the temperature. Dyspnea sometimes sets in, although neither the lungs nor the heart are affected. The skin usually is dry, the face is red, and the conjunctiva injected. The tongue is coated, dry, and sometimes serrated at the edges. There is generally a characteristic buccal fetor. Pharyngitis, rhinitis and slight bronchitis are often present. The patient complains of nausea, and there may be vomiting, especially in children. The nausea in the fulminating cases is generally persistent and accompanied by singultus and epigastric pains. The headache is usually localized in the frontal region, but it may be diffused over the entire head. Insomnia is almost complete during the initial stage, while vertigo and tinnitus are not uncommon. In children convulsions are often noted. But the most obtrusive symptom is backache, which often is already manifest during the incubation period, persisting through the initial stages up to the breaking out of the eruption. The pain is usually located in the lumbar region and is peculiarly severe and "sickening" in character; in some cases it is associated with drawing pains in the legs together with a loss of power, and joint pains suggestive of articular rheumatism and septic disease. Often stiffness and pain in the nape of the neck together with the severe headache raise the suspicion of meningitis. The heart and the lungs are nearly always negative. But the liver may be tender to pressure, though not enlarged. Enlargement of the spleen is generally marked, even in the early stages of the disease. In fact, some authorities find that the splenic enlargement is most pronounced in the early stage of variola vera, while in varioloid palpable enlargement is wanting. The condition of the splenic area, therefore, might be of diagnostic value. The bowels are constipated. The urine is of high specific gravity and is reduced in quantity. Albuminuria (febrile type) may be present; pronounced albuminuria represents an unfavorable sign, since it is generally associated with the type of the disease which develops into the hemorrhagic form. In the female menstrual-like bleeding begins at once, and although this phenomenon is often associated with other febrile conditions, it is particularly characteristic of variola.

Symptoms during Progress of Disease.—A prodromal rash appears on the first or second day after the onset of symptoms and disappears in a few hours. It may be scarlatiniform or morbilliform, either of which may be associated with petechiae. The distribution may be general, but as a rule it involves only the lower abdominal areas, the inner aspects of the thighs, the lateral thoracic region, the axilla, and sometimes the knees and elbows. This feature occurs more often during some epidemics than others, but is generally considered to be present in from ten to sixteen per cent. of cases. Between the third and fifth day—usually in sixty hours—the actual variola eruption breaks out, the severe initial symptoms begin to abate, and the patient feels so much better that he is liable to think that he is at the end of his trouble.

The eruption appears first on the exposed surfaces of the body, i.e., those subject to the greatest irritation—the forehead, the back of the hands, front of the wrists—and within the next twenty-four hours on the face, neck, feet and trunk, in the order mentioned. It also attacks the mucous membranes of the pharynx, palate, mouth and tongue, sometimes appearing in this location before the papules are seen on the skin. It may also early attack the larynx, trachea and large bronchi. A lesion that develops on the mucous membranes appears first as a red macule which soon turns grayish and is surrounded by a red zone due to the formation of a vesicle which soon ruptures. When only a few lesions are present on the mucosa discrete erosions result, but when the lesions are more numerous, more or less deep and irregular ulceration may ensue, simulating diphtheria.

The evolution of the typical eruption of variola is unique, its peculiar interest resting on the regularity with which it passes from one stage to another at certain definite intervals, such as is not seen in any other acute exanthem.

The eruption appears about the third day of the disease as small red *macules*, which in a few hours develop into *papules* about the size of a small pea, generally hard and shotty to the touch. On the fourth or fifth day (second day of the eruption) the papules develop a conical point, the beginning of vesiculation; during the next three days the *vesicle* gradually fills, increases in size until it is circular, tense and umbilicated, owing to the development of a central depression. It reaches maturity on the eighth or ninth day (sixth or seventh of the eruption). The cellular contents now become turbid, owing to the commingling of pus bodies, the umbilication disappears and the lesion again becomes rounded or dome-shaped. Careful examination after pricking of the lesions at this time will show that they are multilocular, since they fail to collapse. On the ninth day (seventh of the eruption) the typical variola *pustule* is seen. A red areola develops around the base of the pustule, the confluence of which, when the eruption is profuse and thickly disseminated, leads to a typical edema of the face, especially around the eyelids, nostrils, lips and mouth. It is at this stage that the characteristic secondary rise of temperature sets in, and at which the suffering of the patient is most intense.

In the favorable cases this fever lasts only a day or so, and on the tenth or eleventh day of the disease (eighth or ninth of the eruption) the pustules begin to dry up and the temperature falls, reaching the normal at the end of the second or the beginning of the third week. The *desiccation* process begins on the face and proceeds in the same order in which the eruption appeared. By the fourteenth or fifteenth day of the disease desquamation will be well advanced on the face. The eruption may be present in its different stages in various parts of the body, but the different stages are never seen side by side on the same part of the body. In other words, unlike the varicella eruption, that of variola does not appear in crops, though it may resemble varicella in that some of the lesions may abort at the vesicular stage.

During the desiccating stage the skin around the lesions, especially on the limbs, may become inflamed, and large, flat pemphigus-like bullae develop. These are filled with a thin yellowish fluid, and as they rupture leave an ulcerous surface on which crusts form. At this stage the temperature may again arise, attended by more or less marked constitutional symptoms. According to the severity of the eruption and the number of lesions this secondary fever may be slight and evanescent, or it may reach a maximum of 102°-103° F. (38.9°-39.5° C.) or more, the height of the fever apparently depending upon the tension in the lesions and the extreme discomfort and irritation they cause, and to some degree also, upon the septic absorption of their contents. The fever continues even after some of the pustules rupture, and persists into the early stages of desiccation.

With the process of desiccation the subcutaneous edema subsides, the suffering is relieved, and although the patient is weak and exhausted, convalescence sets in. The process of encrustation is generally completed in about sixteen days from the onset of the illness, when the crusts begin to fall off. The crusts show a tendency to persist longest on the hands and feet, where small "cores" may remain which often have to be removed with a knife or scissors. These cores are hard, dark brown, or black masses buried beneath the skin, and on puncture evacuate a slimy substance which is readily removed with a needle. During the crusting stage the most annoying symptom is intense itching, and often, unless prevented, the patient will scratch so forcibly as to induce secondary infection. The scratching, however, does not, as is generally supposed, influence the resulting scar. Whether or not the skin scars remain after desquamation is completed, depends upon the character of the suppurative process. If superficial, the pustule dries without leaving a mark, but if the papillary layer has been included in the suppurative process, a scar will remain at its site, due to the replacement of the epithelium by vascular granulation tissue which is transformed into connective scar tissue, leaving the typical pock mark, which often persists during life. In some patients the hair falls out during the crusting stage and even later, but generally grows again, except, of course, where the hair follicles have been destroyed by the suppurative process.

In uncomplicated cases of variola vera complete recovery takes place in from three to six weeks. In the complicated cases, of course, the time is indefinite.

The blood-picture in variola during the incubation period shows marked leukocytosis with polymorphonuclears predominating; later on, in the papular stage, the leukocytes are not increased, and may even be subnormal in number. In the vesicular stage and continuing for several weeks thereafter, leukocytosis is again more or less marked with lymphocyte cells predominating; a very high leukocytosis indicates the presence of some complication. In severe cases myelocytes and normoblasts are present and if found in large numbers are considered unfavorable signs. In vaccinia the blood-count, according to Schatzmann, is analogous to that of variola, the difference being one of degree only,

thus indicating the identity of the two diseases. Erlenmeyer, on the other hand, did not observe the predominance of lymphocytes in vaccinia. He believes the eruptive stage in vaccinia corresponds to the prodromal stages of variola, or that perhaps, owing to the peculiar mode of infection, the skin and the general reaction appear simultaneously.

Diagnosis.—The diagnosis of variola is neither easy nor certain before the typical eruption appears; at the same time it may be said that there is perhaps no disease in which early definite diagnosis is of such primary importance. The general symptom-complex—more or less sudden onset, headache, generalized pains, usually more marked in the lumbar region, nausea, vomiting, fever, with or without a previous chill, delirium, especially in children—is not peculiar to variola only: the addition of a prodromal rash, especially in the absence of a known exposure to variola, still more confuses the diagnosis. In the initial stage the symptoms may suggest *influenza* or *lumbago*, although the latter is rarely accompanied by headache, fever or general prostration: so that it should be easily ruled out. Influenza is not so easily excluded, especially, as may well happen, if both it and variola are epidemic at the same time. Differentiation would then be almost impossible until the actual variola eruption had appeared. If this is not seen on the fourth day a diagnosis of influenza may be safely made. Furthermore, a slow pulse compared with the temperature is also significant of influenza.

The onset of variola may also sometimes simulate *pneumonia*, and, in a certain percentage of cases, stiffness of the neck and delirium may suggest *meningitis*. For pneumonia the character of the expectoration is decisive, while for meningitis, lumbar puncture and the ophthalmoscopic picture should make the situation clear.

Differentiation between *typhus*, as well as *typhoid fever*, may sometimes have to be made. Typhus often during the first three days presents severe backache, and on the fourth day a roseola exanthem resembling the prodromal variola rash. The temperature chart in such cases should remove any doubt, for none of the acute exanthemata presents the characteristic fall of temperature as that seen at the beginning of a variolous eruption. The temperature chart is also a guide in diagnosing typhoid fever, the rise being gradual, while the onset of symptoms, unlike those of variola, is slow and insidious.

The prodromal rash that appears in a small percentage of cases may be scarlatiniform or morbilliform in character. It is comforting to know that the prodromal variolous rash does not appear in children under ten years of age (Ker). In addition, pronounced throat and tongue symptoms together with circumoral pallor are typical of *scarlet fever*, while in variola there are neither throat nor tongue symptoms, the face is more uniformly flushed, the rash is less diffuse and not so distinctly punctate. In *hemorrhagic small-pox*, however, the rash may sometimes be mistaken for those cases of severe scarlatina which present petechial spots and a very vivid rash. It is obvious that in such in-

stances careful isolation of the patient, until the appearance of signs pathognomonic of one or the other disease, is most essential.

The morbilliform prodromal rash of variola can be distinguished from *measles* by the presence of Koplik's spots, but (as Ricketts points out) not by their absence, for the spots may have disappeared by the time the rash becomes evident. On the other hand, the lesions of variola that develop on the mucous membrane of the mouth are apt to be present early, before the papules appear on the skin, and there might be danger of confusing these with Koplik's spots. The former, however, are found chiefly on the palate and the fauces and only to a slight degree, if at all, on the sides of the mouth. It should also be remembered that an erythematous eruption is probably not due to measles unless it is associated with pronounced symptoms of coryza. Furthermore, the onset of measles is not sudden, and is not apt to be accompanied by vomiting, headache, backache and chills.

In doubtful cases the blood-picture may be of value in arriving at a diagnosis. Increased leukocytes with lymphocytes predominating and the absence of eosinophils characterizes the blood in variola, while in scarlatina, eosinophilia is marked, and in measles there are few lymphocytes and no eosinophils during the exanthematous stage. The differentiation is important, inasmuch as in case of death, a certificate of death from measles or scarlet fever, when the actual cause was small-pox, would be apt to lead to serious consequences.

In the papular stage also, variola is liable to be confused with measles, especially as the papules in the latter may be hard and shotty to the touch, like those of variola; while the variola lesions, especially in the modified form of the disease as we see it to-day, may be rather soft, particularly those of only a few hours' growth. The distribution of the eruption in such cases is probably the most reliable guide. The eruption of measles covers the entire body, while in variola the flanks are generally spared, and a papular rash on the face will generally be accompanied by a simultaneous, definite, vesicular eruption on the palate.

Differential diagnosis during the vesicular and suppurative periods in a typical case of variola vera presents little difficulty. But to-day, when the general type of variola is so mild or atypical or so much modified by the more or less general practice of vaccination, the distinction between it and other exanthemata is sometimes exceedingly difficult. This is especially true of *varicella*, which is probably the one disease that more than any other is confused with variola. In the greater number of cases the resemblance is only a superficial one, but frequently the differentiation must be made on more or less delicate indications, indeed, is often impossible even by the most expert diagnostician.

The age of the patient is not significant, for varicella does sometimes occur among adults (p. 223), although variola, owing to early vaccination, is rare among children. The initial symptoms may be a guide, since in varicella the eruption, as a rule, is the first sign of the disease, which is not the case in variola, and generally appears at

the same time with the constitutional symptoms, particularly in children. But in the adult the prodromal stage is often long and severe and presents all the symptoms of variola. It is these cases that enhance the difficulties of differential diagnosis. In varicella the eruption preferably attacks, first, the covered portions of the body, while in variola the eruption appears first on the face and exposed portions, the greater number of lesions appearing on the face, the forearms, and the wrists; on the legs and thighs, if the eruption is profuse, while the abdomen is usually least affected. This is considered by Ricketts one of the most important distinctions between the two diseases. The presence of numerous lesions on the palms and soles would, in his opinion, argue against chicken-pox and in favor of small-pox.

As to the character of the eruption itself: first of all, the variola eruption does not come out in crops, as does that of varicella; secondly, the development of the varicella eruption often is so rapid and so symptomless that it seems to miss the papular stage and is recognized only in the vesicular stage; finally, the shape of the lesions is characteristic. Those of varicella are oval, often irregular and soft and velvety to the touch, while the variolous lesions are round, almost invariably so, and are hard and shotty.

Both diseases may, of course, develop anomalies with regard to all these points, but it is more unusual for varicella to mimic variola than it is for a variolous eruption to imitate varicella, which, of course, is fraught with greater danger.

The distribution of the eruption in such instances again is a valuable guide. Indeed, according to Ricketts, it is finally the distinguishing feature on which the greatest reliance can be placed. This is true even in the cases which present the greatest difficulty, i.e., those in which the eruption is scant, although here the character of the lesions may possibly be a more valuable guide.

The differentiation of the two diseases is of such importance that we find it expedient to use Ricketts' tabular form in summarizing the main differences between the eruption of variola and varicella:

VARIOLA

1. The rash is most abundant on the face; most scanty on the abdomen and chest.

2. The rash is much more abundant on the back than on the abdomen.

3. The rash is more abundant on the shoulders than across the loins, and on the chest than on the abdomen.

4. The rash favors the limbs and, generally, the arms, next to the face.

VARICELLA

1. The abdomen and chest are covered as thickly as the face, or more thickly.

2. The abdomen is covered equally with the back.

3. The distribution is indifferent.

4. The rash tends to avoid the limbs.

VARIOLA

5. The distribution on the limbs is centrifugal.

6. The rash favors prominences, and surfaces exposed to irritation; it tends to avoid protected surfaces, flexures and depressions.

7. The lesions are deep-seated, and have an infiltrated base.

8. The lesions are generally circular in outline.

9. The lesions are homogeneous in character; or if they are heterogeneous they are heterogeneous by law.

10. The vesicles, generally, are multilocular.

11. Frequently some of the vesicles are indented.

VARICELLA

5. The distribution on the limbs is centripetal.

6. The rash behaves indifferently.

7. The lesions are superficial and the base is not infiltrated.

8. The lesions frequently have an irregular outline; when they lie near a flexure they are apt to be oval or elongated.

9. The lesions often are not homogeneous; and the want of homogeneity bears no relation to the sizes of the lesions and to their situation.

10. The vesicles, generally, are unilocular.

11. The vesicles are never indented and seldom dimpled.

Among other pustulous eruptions which may resemble variola may be mentioned *syphilitic eruptions*, *acne*, *impetigo contagiosa*, and the *pustulous exanthemata of septic diseases*. The Wassermann reaction and the history of the case should exclude syphilis, while in acne and impetigo the absence of initial symptoms preceding the outbreak of the eruption should serve to make the proper diagnosis. In addition to this, the vesicles of impetigo are unilocular, and the redness surrounding the sore is not so marked as in variola. *Rashes due to digestive disturbances or to drugs*, bromids, iodids, etc., can be recognized by the absence of initial symptoms and the history of dietary indiscretion, or the administration of certain drugs.

In *pneumococcic septicemia after pneumonia*, much confusion may be caused by the presence of a pustulous eruption on the back, the chest and the extremities, but the distribution of the sores and the absence of a history of exposure to variola should prevent an error of diagnosis in such instances.

The vaccination test on the cornea of the rabbit is often resorted to in suspected cases. Inoculating the contents of a variola pustule into the rabbit's cornea produces a typical lesion in about thirty hours. at first a thickening of the epithelium, which in a day or two develops into a sore, stained sections of which present Guarnieri bodies.

The final test, however, is convincing evidence of vaccination. Successful vaccination within half a dozen years, at least, or revaccination at any time, or a successful vaccination during the early stages

of the disease—especially after the third day of the eruption—may be taken to indicate that the ailment is not small-pox.

Complications.—The complications of variola are generally related to the severity of the skin lesions, especially during the suppurative stage, and are due to pyogenic infection of the skin, the eyes and the mucous membranes of the nose, mouth, the throat and the respiratory tract.

The presence of a *pustule on the eye* may lead not only to severe conjunctivitis, but also to ulceration of the cornea followed by opacity, perforation and even panophthalmia. Severe cases may lead to permanent blindness.

More or less serious *ear trouble* may also complicate variola. The external canal as well as the tympanum and the mucosa of the eustachian tube sometimes become congested and swollen, and purulent otitis media and even mastoiditis or other sequelæ of otitis media may occur.

The *eruption on the mucous membrane of the nasopharynx* may lead to phlegmonous inflammation of the esophagus, tongue and fauces, the latter sometimes suggesting diphtheria, or it may lead to an ulcerative condition of the larynx with its attendant sequelæ; there is nearly always some hoarseness, although complete loss of voice is rare. When it does occur it is a bad prognostic sign. Edema of the glottis also often complicates variola, and may be severe enough to demand tracheotomy.

The *damaged condition of the skin* may lead to bed-sores, superficial abscesses and boils, unless great care is taken to prevent them: while cellulitis, erysipelas and tetanus may appear during the stage of encrustation and result in death.

The *most important complications of variola*, however, are those that involve the *respiratory passages*. Bronchitis is decidedly not uncommon and may be serious and develop into bronchopneumonia. Lobar pneumonia and pleurisy often accompany variola: while heart affections—pericarditis (serofibrinous or purulent) and myocarditis—are sometimes met with. Adenitis, cervical and axillary, and orchitis (in the male) also frequently complicate variola. The latter is by some authorities regarded as part of the symptom-complex of the disease, but others feel justified in considering it a complication, since changes have been observed postmortem that suggest that the orchitis develops during the evolution of the eruption. Small, hard nodules may sometimes be palpated (*intra vitam*) during the pustular stage.

Nephritis is not unusual. *Paralysis* is sometimes reported. It is, however, usually transitory and disappears in a few weeks. It is generally interpreted as a peripheral neuritis, but (as McClure points out) is more likely the result of the effect of the toxin on the spinal cord and the meninges. Cases of *paraplegia* and *hemiplegia* are also recorded, but are very unusual.

Clinical Varieties.—The clinical course of variola is determined by the severity and the character of the eruption, the disease accordingly presenting several clinical varieties, the most malignant of which is *variola hemorrhagica*, occurring in two forms: *variola hemorrhagica*

purpura (black small-pox) and variola hemorrhagica pustulosa. Less malignant is the type known as *variola vera* in which the lesions may be confluent, semiconfluent or discrete, the latter gradually merging into the third variety, known as *varioloid*, a modified form which, in some instances, is so aberrant as to omit the eruption altogether, being then known as *variola sine exanthem*.

Before vaccination was as commonly practiced as it is to-day among intelligent and civilized people, the hemorrhagic type and the malignant forms of variola vera were much more frequent than they now are and were more prevalent in some epidemics than in others.

VARIOLA HEMORRHAGICA.—The hemorrhagic forms of variola seem preferably to attack young people and pregnant women. The latter, if they survive long enough, usually abort. The two forms are manifestations of different degrees of the severe toxemia—in *purpura* the hemorrhage into the pocks from the mucous membrane occurs during the eruptive stage, while in *pustulosa* it takes place during the vesicular or pustular stage. The initial symptoms in either are severe.

Variola Hemorrhagica Purpura.—On the evening of the second day, or on the third day, in the purpuric form, a diffuse hyperemic rash appears on the body, developing especially in the groins, starting with small punctiform hemorrhages which gradually increase in size; at the same time the conjunctivæ are more or less ecchymotic and there may be hemorrhage from the mucous membranes. The skin assumes a purplish or even a plum-colored hue, and the edema of the face, together with large conjunctival hemorrhage, and sunken appearance of the cornea, gives the patient a truly ghastly aspect. Death generally results in three or four days, but may set in even before the rash appears.

Variola Hemorrhagica Pustulosa.—The clinical picture of *variola hemorrhagica pustulosa* is not much more encouraging. The fatal course may be delayed to the seventh, eighth or ninth day, but is generally run in three to four days. The earlier the hemorrhage takes place the greater is the danger. When the lesions succeed in progressing to the pustular stage, hemorrhage may occur between the lesions or at their bases, the prognosis being a little more favorable when the latter is the case.

VARIOLA VERA.—*Confluent Types.*—In the confluent types, as their name indicates, the lesions are more or less closely sown so as to adhere or to merge one into another during the pustular stage. This refers particularly to the eruption on the face and the exposed surfaces; on the body itself the pocks are, as a rule, discrete. The evolution of the eruption is generally rapid, with a very rapid dissemination over the body, especially marked on the face, which becomes edematous and distorted.

Involvement of the mucous membranes leads to complications which in turn unfavorably affect the temperature. The condition progresses from bad to worse and the end generally comes with associated symptoms of general sepsis.

When recovery takes place convalescence is slow and protracted.

Desiccation of the confluent lesions is retarded, owing to the reformation of suppuration in the very diffuse eruption. The normal process is also interrupted by the development of abscesses and furuncles. After the primary desquamation thin crusts often form again and again before the final healing of the lesions takes place. The lesions on the mucous membranes also heal very slowly; and fever, owing to complications, is apt to persist into the third week of the disease.

Discrete Form.—In the discrete form of variola vera the lesions are fewer in number and the disease is not so apt to be fatal, its malignancy depending upon the number of lesions and the presence or absence of complications. The skin presents the same inflammatory edema, but, as the pustular stage is reached, the temperature falls, the general condition improves, and in uncomplicated cases convalescence sets in toward the end of the second week.

VARIOLOID.—The benign variety of variola, known as varioloid, is by some authors made to include all mild or aberrant forms of the disease, while others restrict the term to those cases that have been modified by vaccination.

Varioloid differs from variola vera in running a shorter and more benign course after the eruption once appears. The incubation period is the same, but the period of invasion may be longer or shorter than in variola vera, while the symptoms may or may not be severe, and in no way indicate the clinical type that the disease will assume. The latter can sometimes be foretold by the prodromal rash which in variola vera is generally petechial, while in varioloid it is more likely to be erythematous or morbilliform. It is the character of the eruption, as we have seen, that finally determines the history of the disease itself. In varioloid the temperature, if it has been high, falls rapidly during the eruptive period, reaching the normal on about the fourth day, without any secondary rise at the suppurative stage, except in very rare instances. The eruption may vary both in the order and extent of distribution and in its evolution. Instead of regularly beginning on the face or exposed surfaces it often appears first on the trunk or simultaneously in different parts of the body. The number of efflorescences may vary from a very few discrete pocks to a profuse eruption diffusely spread over the skin surfaces. The single pocks, beginning as red macules, are quickly transformed into papules, many aborting at this stage. Others go on to vesiculation and abort at the beginning of the pustular stage, and some very rapidly go through the pustular stage—a fact that often adds to the difficulties of diagnosis. The vesicle begins to fill about twelve hours after the macule appears, and on the third day (of the eruption) shows signs of suppuration which nearly always is superficial. The areola surrounding the pustule is small without any evidence of inflammatory or edematous swelling. Desiccation begins on the fifth to the seventh day (of the eruption); or earlier in the abortive efflorescences. The pustules simply dry up without rupturing, and leave a thin brownish crust which, being superficial, falls off easily. It is only in the buried crusts on the palms and soles that desquamation is

apt to be slow. Slight prominences and pigmentation which remain after desquamation disappear in a few weeks without leaving any trace of the disease.

The mucous membranes are often affected but not so severely. The visible pocks are few in number, and although catarrhal inflammation of the buccal mucosa, dysphagia, hoarseness and coryza are present, they are not so annoying as in variola vera, and never give rise to serious ulcerative and necrotic processes. This type of the disease is probably not so infectious and contagious as variola vera, since it practically never attacks an individual who has been successfully vaccinated, even at a remote period.

VARIOLA SINE EXANTHEM.—Some exceedingly mild forms of varioloid, in which only a few pocks develop, form the transition type to variola sine exanthem, in which there is no sign of the eruption on the skin or on the mucous membranes. The etiology of the disorder rests altogether on circumstantial evidence. Often a person with somewhat defective immunity, possibly from a very remote vaccination, who is known to have been exposed to small-pox contagion, develops symptoms so typical of the invasion period that the eruption is naturally expected to appear on the third day, but fails to do so. Instances of this kind have been observed during certain epidemics in sufficient numbers to warrant the inclusion of the form as a variety of varioloid. Marked backache in these cases should arouse the suspicion, while the appearance of a prodromal rash should establish a diagnosis of variola sine exanthem; for often the disease is not recognized except in its effects, such cases having been known to form the source of infection in a case of variola vera.

Treatment.—**PROPHYLAXIS.**—Prophylaxis against variola is comprised in the one word—**vaccination**. With this definite preventive measure at the command of medicine for more than a century, the beneficial value of which is beyond estimation, the subject of variola should to-day be a matter of historical interest only. Unfortunately, however, the light has not yet penetrated into certain quarters and cases of variola do occur among unvaccinated individuals or among such persons who have to some extent lost the immunity acquired by a remote vaccination.

The question of the *persistence of the immunizing effects of vaccination* is an important one. There is no doubt that it establishes life-long immunity to a certain degree, but some persons show a greater predisposition to the disease than others, and at a more or less remote period the protective value of vaccination begins to diminish. The thirtieth year of life is generally regarded as the period at which this becomes evident—a fact that has been recently confirmed through the opportunities afforded for the study of this question during the world war. It appears that “cradle” vaccination and revaccination at puberty are effective in the vast majority (about 95 per cent.) of individuals up to about the fourth decade, the effects beginning to decline after the thirtieth year, so that revaccination of all persons between the thirtieth

and fortieth years is advisable. Among 1,000 (500 males, 500 females) individuals, Gins obtained 30.4 per cent. successful revaccinations among those between thirty-one and thirty-five years, 62.7 per cent. among those between thirty-six and forty years of age, and about 65 per cent. among those beyond the fortieth year. A decided increase is also seen in the severity of the disease (in vaccinated persons) acquired after the thirtieth year as compared to that acquired before that period. Among 58 cases that contracted variola between the ages of fifteen and thirty years, 60 per cent. developed mild cases, 36 per cent. moderate, and 16 per cent. severe cases, with only one death in the series. Among a group of 328 individuals over thirty years of age who fell ill, 68 per cent. were beyond the fortieth year; of these, 33 per cent. developed mild, 43 per cent. moderate, and 24 per cent. severe cases, with a death rate of about 13 per cent. For the years between thirty-one and forty, the cases were mild in 52 per cent., moderate in 29 per cent. and severe in 16 per cent., with a death rate of 4 per cent.

Second only to the prevention of small-pox by vaccination and revaccination is the importance of **preventing its spread**. Notification to the public health authorities and **isolation** of the patient are the first steps to be considered. Wherever possible, prompt removal of the patient to an isolation hospital is demanded. The hospital, whenever feasible, should be situated in a sparsely settled district, since the disease is carried by the air and by insects, and small-pox hospitals have often been suspected of forming the foci for the spread of the disease. After the patient has been thus placed in strict quarantine, vaccination of all contacts and suspects should be rigidly enforced, since variola is highly infectious from the moment of the appearance of the initial symptoms. The patient's whereabouts during the two weeks (incubation period) prior to his illness should be investigated, in order to discover any possible unreported contacts. Successful vaccination or revaccination of these persons, if done within three days of exposure, will usually prevent any secondary outbreak, and if done as late as the sixth day, will certainly modify the course of the attack. Contacts who fail to present evidence of recent successful vaccination should be kept in quarantine for fourteen days, or until all danger of developing the disease has passed. Those, however, who show satisfactory vaccination marks of comparatively recent date should be kept under observation, but may be allowed their liberty; for it is as sure as anything in medicine that they will not contract the disease. The economic loss and great inconvenience attendant upon maintaining a strict quarantine should be taken into consideration by the health authorities and the physician, and should not be imposed upon those whom experience has shown to be practically immune to variola.

The patient's **home should be fumigated**, and the furnishings of the room and the room itself **cleansed with soap and water**, and **renovated**, if possible. This renovation is more essential in cases of small-pox than perhaps in any other acute infection, owing to the extreme tenacity of the virus of the disease.

The patient should be kept under **strict quarantine** until all the crusts have separated, especially those (buried cores) on the palms and soles. When very persistent, the desquamation process can sometimes be hastened by means of **warm soap and water baths**.

Only such persons should be employed to attend a small-pox patient who have been properly protected by vaccination or by revaccination before entering the sick-room. In reality it is good practice routinely to **vaccinate any one who is assigned to attend the patient**. The nurse should **disinfect** everything that comes in contact with the patient, such as bed and body linens, eating utensils and dishes. Bandages and dressings should be burned, and the excreta disinfected before being carried from the room. General rules, as given in the chapter on Scarlet Fever (pp. 257-258), should be observed in hospital cases as well as in those treated in the home.

The strictness of quarantine should in no way be relaxed in a case of *varioid*. The latter condition may be as infectious as *variola vera*, and may give rise to any of the more severe and fatal forms.

Varioid and the milder forms that are generally met with to-day need very little treatment. Isolation provides the necessary rest which is about the only thing the patient will require after the initial fever has subsided.

GENERAL TREATMENT.—The general treatment of variola is purely **symptomatic**. The patient should be made as comfortable as possible. Plenty of **fresh air, a comfortable bed**, with light bed-coverings supported by a frame or cradle, and frequent change of sheets are essential. A **water-bed** often proves serviceable in relieving the discomfort of the numerous hard lesions.

In the *præruptive stage*, or the period of initial fever, the severe headache can be relieved by **phenacetin**, or **cafein**, cautiously given; and for the backache, **aspirin combined with codein** is useful; joint pains should be treated with **hot fomentations or poultices**; **dry cupping** has also given satisfaction. Thirst should be relieved by copious draughts of **water** with or without the addition of **lemon juice** or in the form of the Imperial Drink (p. 267). For the chilliness the use of **hot water-bags or bottles** is indicated. For the fever at this stage **cold sponges or cold packs**, according to the degree of fever and the presence or absence of nervous symptoms, will be found efficacious.

Diet during the febrile stage should be limited to liquid nourishment, milk, buttermilk, albumen, water, etc. After the initial fever subsides advantage should be taken of the afebrile period to push the diet to include as much nourishing solid food as the patient will take, such as steak, chops, eggs, milk and the more easily digested vegetables. Thus fortified, the patient will be better able to combat the severe struggle that is in store for him during the stage of suppuration. During the secondary fever the diet is again limited to the customary febrile régime. Sometimes, owing to the presence of the specific lesions in the mouth and throat, there will be difficulty in swallowing and the diet will have to be limited to liquids throughout the illness. It is important

for the patient to have as much nourishment as possible. Feeding should be regular at two or three-hour intervals, including the night, if the patient is awake. We would suggest milk—either plain or peptonized, with the addition of thin gruel, or in the form of milk punch—eggs, eggnog, broths or beef juice, four to ten ounces pressed from fresh cut beef, and if desired, mixed with milk. Where there is difficulty in swallowing, the liquids are better given cold: rectal feeding may have to be resorted to in severe cases, although it is not apt to be successful, possibly on account of the presence of lesions in the rectum.

Orthoform, one grain (.065 gram), given just before feeding, may be helpful; failing this, the throat may be painted with a 1 per cent. solution of **cocain hydrochlorate**, which usually will remove the difficulty of swallowing. **Alcohol** is well borne by small-pox patients, and in the severe cases may be given in the form of brandy or whiskey, in milk, or in a small amount of glycerin or syrup and water to avoid irritating the throat; in the mild cases alcohol is not usually indicated.

During convalescence the régime should again be liberal and the appetite stimulated, if necessary, by **tonics** containing strychnia and alcohol.

For the *secondary fever in its early stages* **cold baths** in the form of **packs and sponging** will prove of value; but during the *later or suppurative stage* **warmth** is indicated. This is usually given in the form of the **continuous warm bath** for several days at a time, with the patient placed in a sort of cradle in the tub, the water to be kept at a constant temperature of 95° F. (35° C.) It is important not to allow the water to cool, as a lower temperature may cause the patient to become depressed. *Ruhräh* considers this one of the best means of treatment at our disposal. It lessens delirium, should it be present, keeps the skin clean and oftentimes lessens absorption and prevents the formation of scabs and of suppuration beneath the scabs.

Delirium is treated in the usual manner by the use of **sedatives**—bromids, with or without chloral or morphin. The administration of a **cathartic** oftentimes assists in quieting the patient. The delirium may be severe and may necessitate **restraint**, but this should be resorted to only when absolutely necessary, in order to avoid possible rupture of the pustules and injury to the severely traumatized skin by tugging and pulling at the restraining bands.

For *insomnia*, **hypnotics**, such as veronal or trional, may be of use. Or sometimes one or two large doses of **whiskey** may bring the desired sleep.

There are few, if any drugs, that abort or alter the attack in every instance. Some authorities, Ker, for example, find **salol**, 10 grains (0.65 gram) useful if given every four hours as soon as the eruption appears. In some instances this has brought about a more rapid evolution of the eruption to the stage of pustulation, the latter being incompletely developed. This writer makes the reservation, however, that nearly all cases so treated had been vaccinated in infancy and therefore have retained a certain degree of protection. The drug is sufficiently harmless to be worth a trial.

In line with the modern use of colloidal metals in the treatment of infections, gold has proven useful in some instances. Septét and Manet used intravenous injections of **colloidal gold** in five cases of variola confluent and succeeded in obtaining a reduction of the fever during the suppurative stage which, in spite of the serious condition, never rose above 104° F. (40° C.). In one case suppuration was altogether prevented, while in another (secondary hemorrhagic variola) the cutaneous symptoms were rapidly controlled and crusting encouraged. Complications during convalescence were limited to abscess formation (two) in one instance, and in another to abscess and adenitis; while in the cases not treated with the gold, convalescence was interrupted by severe furunculosis, multiple abscesses (19 in one case), diffuse phlegmon, erysipelas, etc. No visceral disturbances followed the injections which were given, one dose daily of 1½ c.c. and 1 c.c. respectively, on two successive days, followed on the fourth day by 2 c.c. of the colloidal gold, the latter being the largest amount that was given. The administration was stopped as soon as the temperature fell to 100.4° F. (38° C.). Each injection was immediately followed by an injection of **camphorated oil**, for the purpose of obviating cardiac symptoms during the reaction.

Owing to the swollen condition of the tissues it may sometimes be difficult to give the injections; in two cases in this series it would have been altogether impossible to do so had the patients not been treated before the eruption broke out.

Treatment of the eruptions is directed toward keeping the lesions clean and intact. Welch and Schamberg recommend painting the confluent parts with a freshly prepared **tincture of iodin**, pure, or, if desirable, diluted, repeated daily or every other day. This we find secures early separation of the scabs, reduces the tendency to abscess formation and lessens the inflammation of the skin in the later stages. Others apply a solution of 25 per cent. **alcohol with boric acid**; and still others advise spraying with **alcohol alone or combined with some other antiseptic solution**, or with **ether and bichlorid**, 1/3,000 or 1/5,000. During the period when the lesions begin to rupture **compresses of permanganate of potassium** frequently changed will serve to keep the skin clean and remove the discharging pus which, if allowed to dry, is apt to lead to formation of crusts and abscesses beneath them.

Ointments and dusting powders are not indicated during the early stages of the eruption, but when the crusting period sets in, a **bland ointment** will be found useful in reducing suppuration, keeping the scabs soft and hastening desquamation. **Warm soap and water baths** several times daily serve to aid in the separation of the scabs, and any of the dusting powders will relieve the irritation that results after the scabs fall off. **Alcohol and alum water**, judiciously used, will serve to harden the tender skin.

Should *erysipelas* supervene it is best treated by wet dressings. *Abscesses and boils* should be incised and drained. *Bed-sores*, or *gangrene of the skin*, should either develop, are treated in the usual manner.

One of the most aggravating symptoms at this (crusting) stage is the *violent itching*. It often causes insomnia and marked nervous symptoms, while the consequent violent scratching increases the chance of secondary infection. It can be treated by **spraying**, with alcohol with or without menthol ($\frac{1}{2}$ -1 per cent.); or by **sponging** with carbolic acid water ($\frac{1}{40}$); or by the application of salicylic acid, or of ichthyol diluted with glycerin. Either of these may also be used in the form of ointments, not in the early stage, but later on.

Anything that prevents suppuration also favorably affects the resulting scarring. This is best accomplished by the **tincture of iodin**, already mentioned, while the softening of the scabs, which, if removed, is supposed also to reduce the scarring, is often hastened by the use of an ointment composed of **bicarbonate of soda** 2 drams (8 grams) and **petrolatum** 1 ounce (30 grams), as recommended by Welch and Schamberg. Ruhräh advocates frequent bathing in water, to which some antiseptic is added, such as **bichlorid of mercury** ($\frac{1}{10,000}$) or **alum** ($\frac{1}{1,000}$). One pound of the latter to a tub (500 liters) of water would be an approximate proportion.

The small-pox patient emits a disagreeable odor which is annoying to himself as well as to his attendants. It can be controlled by frequent bathing in water, to which **permanganate of potassium** has been added.

In former times small-pox was one of the most fruitful sources of blindness, mainly due to the omission of prophylactic care of the eyes. It is therefore important to make the toilet of the eyes part of the routine treatment of variola. *Mild conjunctivitis* will require merely **irrigation of the eyes** three to four times daily with **salt solution** or **boracic acid solution**, and anointing the lids at night with an ointment of **yellow oxid of mercury**, $\frac{1}{2}$ grain to $\frac{1}{2}$ ounce (30 milligrams to 15 grams). In the *severer cases* this should be supplemented with **instillations of argyrol**, 10-25 per cent., while for *very severe conjunctivitis* **cold compresses**, one hour at a time, three times daily, will be necessary.

Keratitis should be treated with **irrigations of boric acid**, **instillation of argyrol**, the application of the ointment of **yellow oxid of mercury** (as above), and also **atropin** in a one per cent. solution, one or two drops to be instilled three times a day. In addition to this, the more severe cases will require applications of hot compresses one hour at a time, three times daily.

Ulcers that are deep and threaten to perforate should be gently touched once a day with pure **carbolic acid** or with **tincture of iodin**. And for clearing up corneal opacities it is well to instil **dionin**, beginning with a 4 per cent., and gradually increasing to a 10 per cent., solution, two drops twice daily, and to apply gentle **massage** to the cornea with the ointment of **yellow oxid of mercury**, 1 grain-2 drams (.065 gram-8 grams).

The *throat condition* which often is annoying can be relieved by the use of **cooling drinks**. The *mouth* should be kept clean by frequent washings with any of the **bland antiseptic washes**, of which **permanganate of potash**, $\frac{1}{4000}$, is perhaps the most efficacious, according to

Ruhräh. The *tongue and gums* can be gently swabbed with a **mixture of glycerin, boric acid and water**. If the inflammation of the tongue is severe it usually yields to painting with **glycerite of tannic acid**, but **incision** may sometimes be required. Severe *edema of the glottis* may require **tracheotomy**, which often is particularly difficult to perform on account of the large hemorrhage that is apt to ensue when the tissues of the neck are very much swollen.

For the treatment of the *unsightly and disfiguring scars* remaining after an attack of variola, Unna, Jr., finds the use of **carbon-dioxid snow** in short doses—three, five to ten seconds, according to the individual skin reaction—the most useful. The technic, however, is a delicate one and requires the services of a skin specialist. **Electrolysis** is also recommended by Unna for treating the more prominent scars, while chemical treatment with **thiosiamin and its derivative, fibrolysin**, has also been of service in his experience. The former is applied in the form of a salve, and the latter in subcutaneous injections. Their use favors resorption, as do also **plasters composed of salicylates and mercury**.

The effect of the color red in the form of hangings and curtains about the patient has been known since the early thirteenth century. Finsen, in our time, applies the method in the form of **red-light treatment**. Reports of the results are so lacking in uniformity as to raise considerable doubt in regard to its value. Finsen believes that the exclusion of the chemical action of actinic rays must necessarily diminish the severity of the inflammation and lessen the number of lesions that may develop. He places the patient in what is practically an unventilated, photographic dark-room, from which all but the red rays are excluded. Indeed, some authorities think it necessary to test the glass that is used in order to make certain that no other light enters. The mental effect on the patient confined in such a room is shown in psychic disturbances, restlessness and delirium.

Dreyer attempts to overcome this undesirable effect by excluding the actinic rays more directly by the use of dressings saturated with permanganate of potash, which gives the red coloring and at the same time acts as a disinfectant and a deodorant. He claims to have observed a decided diminution of suppuration, absence of odor and reduction both in severity and duration of the suppuration. This method presents the great advantage of permitting the use of that most valuable therapeutic agent, fresh air, and at the same time obviates the unpleasantness, both for the nurse and patient, of the depressing effect of enforced seclusion in a darkened room.

SERUM THERAPY.—Serum therapy has been suggested and tried, but has not met with success, owing mainly to the enormous amount of serum required, which according to Thomson and Brownlee, is about one-fiftieth part of the body weight for the adult and about one-twentieth for the child. These authors used the serum of immunized heifers which they found, if injected into another heifer recently vaccinated, provided a certain degree of immunity against vaccination.

The use of serum from a recovered variola patient has also been

tried. Although a rational method, it has not met with success; the amount of serum obtainable is small and the results not satisfactory.

Prognosis.—Various factors determine the prognosis of variola. As mentioned in discussing the clinical varieties, much depends upon the character of the specific lesions, and it may be stated here that the danger is in direct proportion to the number of lesions on the face and hands. The fatal character of the hemorrhagic varieties has already been alluded to. In addition to this, there enter the age and condition of the patient and the efficacy of vaccination. Children are more apt to succumb than adults. During the epidemic in Montreal during 1884-1886, over 85 per cent. of deaths occurred among children under ten years of age. As already stated, pregnancy unfavorably influences the course of the disease; naturally, also, intemperate habits and debility are not without their effects. Complications—particularly pharyngitis, laryngitis and bronchitis—often are the direct cause of death. But it is the unvaccinated that supply the greatest number of fatalities in variola. In Welch's collected statistics of 5,000 cases occurring during the epidemic in Philadelphia from 1870-1874, the total death rate was 31.2 per cent.; of this number, 54.18 per cent. occurred among unvaccinated against 1.29 per cent. among vaccinated individuals. The death rate depends upon the form of the disease that prevails. In the hemorrhagic form, recovery is very rare; in the confluent form, in the unvaccinated, the mortality may be as high as 50 per cent. The type of the disease as we now see it is eminently benign, complete recovery without any permanent after-effects being the general rule.

In the severe cases of variola pitting from destruction of the skin often results to such a degree as to produce loathsome disfigurement of the face.

Blindness, as already stated, has been known to result when keratitis with sloughing has complicated the illness.

Pathology.—Councilman describes the histological changes in the skin in variola as due to degeneration of the epithelial cells and exudation into the degenerated part. Degeneration begins in the nuclei of the epithelial cells and is associated with a reticular degeneration of the cytoplasm which may affect all of the lower cells of the epidermis, the result being a characteristic multilocular pock or pustule. This development may be confined to the epidermis or it may also involve the corium which then forms the base of the pustule. The smallest visible papules are due to exudation which, together with cell degeneration, sets in early. According to Councilman, "the earliest visible lesion is really a vesicle, but the exudation enclosed in a number of small spaces does not give the swelling the macroscopic appearance of a vesicle." Leukocytes appear later in the exudate, being attracted by the necrosis. Toward the final stage of the pustule the cells in the exudate, as well as in the degenerated epithelium, break into fragmentary indefinable granular masses.

The exudate in young vesicles rarely contains red blood-corpuscles, although a few are sometimes present in the pustule. Only a few eosino-

phils are found in the exudate in any of the stages. Few polynuclear leukocytes are found in the blood in variola. This can hardly be explained by the paucity of these cells in the skin lesions since, in the lesions in the lungs and mucous membranes which are due to streptococcal infection, the exudate presents the usual cell character.

Bacteria are generally absent in a microscopic study of the vesicles and the pustules. Councilman, in but a few sections of the numerous ones studied, found a few cocci, usually in chains or pairs, occurring more frequently in the corium than in the epidermis. But in no instance was their relation to early epithelial degeneration such that they can be regarded as the causative factor of the disease.

The specific organisms, according to Councilman, are probably brought to the skin by the blood. They enter the epithelial cells at a single point which forms the starting point of the lesion. In purpuric small-pox the organisms reach the skin in larger numbers, so that the condition which ordinarily is found only at the primary focus of vesicle formation is extended over a larger portion of the epidermis.

Repair of the lesions sets in early. The process takes place by absorption and drying up of the fluid portion of the exudate and degeneration of the epidermis, during the course of which the "residual mass of degenerated epithelial cells, leukocytes and debris enclosed between two layers of horny epidermis, the old and the newly formed, is exfoliated."

The lesions, except those on the palms and soles, generally show umbilications, due to no one cause, but in a measure to the primary, hyaline, fibrous degeneration of the epithelial cells, the central and primary point of the lesion, which prevents distention at this point, and partly also to greater adherence of the cells at points where sweat glands and hair ducts pass through the epidermis.

The lesions on the mucous membranes develop in the same way as those of the skin, except that, owing to the absence of a horny layer, the degenerated cells are cast off, so that the specific character is seen only in its early stage, the vesicle being rarely seen and the pustule never.

In addition to the specific lesions there are other non-specific ones which, at autopsy, are frequently found on the soft palate and the uvula, consisting mainly of superficial loss of substance with deep necrosis of the underlying tissue, and containing streptococci and polynuclear leukocytes, numerous when compared to those in specific lesions.

The presence of specific lesions and erosions is often noted post-mortem in the upper respiratory tract and on the tonsils, the soft palate and in the nasopharyngeal region, and extending to the larynx, the bronchi, sometimes also on the uvula and the vagina.

Bronchitis is the most common lesion associated with variola, and is usually attended with more or less extensive bronchopneumonia, affecting both the large and the small bronchi. In fact, pulmonary involvement is the most frequent and the most serious complication of variola and often is sufficiently pronounced to cause death without the aid of the specific disease itself. Different varieties of pyogenic cocci

are constant findings in these cases, streptococci and pneumococci being the most frequent, in the order named.

The digestive tract is comparatively free from specific changes. A few typical efflorescences may develop on the esophagus, but the stomach and intestines are not affected, although occasionally a few pocks develop on the lower part of the rectum. The changes that are found in the gastro-intestinal tract are mainly catarrhal, or in the hemorrhagic type of variola, hemorrhagic from extravasation into the mucosa.

The heart, when death occurs at the suppurative stage, shows a lax myocardium and slight indications of fatty degeneration. Endocarditis is seen only in septic cases.

The liver is enlarged, most markedly so in the pustular and crusting stage, and postmortem shows cloudy swelling and evidence of fatty degeneration. Cloudy swelling also marks the changes in the kidney which are found in all cases of variola, and which may be seen at any stage of the disease. Glomerulonephritis is also observed and, clinically, develops during convalescence. Enlargement of the spleen is especially pronounced in cases that die early. Its capsule is tense and shiny, the consistency of the organ being much softened and its color darkened. In the later stages these changes often disappear.

The testicles also show the same disseminated foci of necrosis in the interstitial substance, in the form of dense, yellowish areas, varying in size from that of a pinhead to that of a pea. This change in the testicles is one of the very pronounced characteristics of variola in the male.

Neerotic changes were noted by Chiari also in the bone-marrow during the eruptive period; these he has designated as *myelitis variolosa*. To these changes, some authors attribute the severe lumbar pains that characterize the disease. Muir, in a later study, paid great attention to the blood and bone-marrow. He found a marked diminution or total absence of polymuclear cells—a fact which Councilman was subsequently able to confirm.

Historical Summary.—The history of variola is the history of perhaps the most constant, extensive and malignant scourge with which mankind has been afflicted. The early origin of the disease is obscure. Although Hippocrates, Galen and other ancient writers describe an eruptive disease which may be small-pox, the omission of any mention of the characteristic pock marks by these authors as well as by later Greek and Latin writers, makes it more likely that the description refers to the plague and not to small-pox.

Probably the first definite mention of variola is contained in ancient Chinese medical literature. A memorial (written from memory and found in the Royal Museum at Peking by some missionaries) contains an account of the disorder, together with the description of the fever and the evolution of the eruption into pustules which increase, suppurate, flatten and form crusts. According to this account the disease was introduced into China during the Tcheou dynasty (1122 B. C.), and

since the Ssong dynasty (590 B. C.) had been combated by the use of inoculation of the small-pox material.

The disease was also known to ancient India, the inhabitants of which are said to have worshiped a goddess, Patraglia, who presided over the small-pox.

Both among the Chinese and among the Brahmins of India the custom of variolation was practiced from earliest times, the process among the latter being entirely in the hands of the priests and attended with all kinds of religious ceremonials.

Variola is also supposed to have been prevalent from time immemorial among the Negroes of Central Africa, whence it probably spread by way of the Red Sea, and from there extended to the Arab tribes, appearing (about 569 A. D.) among Abyssinian troops who were besieging Mecca, and so depleted their numbers as to compel them to raise the siege.

The most accurate early description of variola is that of the Bagdad physician, Rhazes, dated about 910 A. D.; but to Avicenna, the Arabian physician (980-1037), belongs the credit of being the first to recognize a difference between small-pox and measles. At about this time also the term *poca*, the Anglo-Saxon equivalent for variola, appears for the first time in a tenth century leech-book attributed to an English physician named Bald. After the introduction of variola into Arabia it became endemic there and appears to have spread to neighboring regions, extending to Asia Minor, North Africa and probably thence to European countries.

According to the writings of one Sigbert von Gemblours, variola appeared in what is now known as France in about the year 541, the epidemic of that year being also described ten years later by Gregory of Tours, who also gave an account of a similar outbreak that occurred in 580 to 582.

From the eleventh century onward an ever-increasing number of records contain descriptions of epidemics of small-pox, the best known of which is that of Constantius Africanus of Carthage, who at Salerno acquainted the physicians of that region with Arabic medicine.

During the twelfth century the crusades with their tremendous outpourings of various peoples were largely instrumental in spreading the disease, the epidemics of these times being of particular virulence.

The Normans are supposed to have introduced variola into England about 1241; at the same time it is also reported from Denmark. On the continent the disorder seems to have become prevalent in Germany in 1493, having probably been imported from the Netherlands; somewhat later it appeared in Russia and Sweden. Epidemics of unusual virulence are reported during 1546-1589 from Italy, France and Holland.

In America, small-pox made its appearance not long after the landing of Columbus. It is reported in Hispaniola (now San Domingo) in 1517; whence it spread to Cuba and the Antilles, and from Cuba to Mexico, through the medium of a Negro slave among troops captured by Navarez and landed in Mexico as prisoners of Fernando Cortez. The

ravages of the epidemic that originated in this way in Mexico beggars description. In a short time three and one-half million people are said to have succumbed to the disease.

Once having gained a foothold in Mexico, it was an easy matter for small-pox to spread to other American countries. In 1710, about 60,000 persons are reported to have died of the scourge in Quito, the capital of Ecuador. In North America the African slave trade afforded an additional favorable opportunity for the continued prevalence of variola, a circumstance considered by some to be an important factor in the extermination of the Indians of North America.

Thus no region seems to have been exempt from the ravages of this fearful scourge which respects neither age, nor sex, nor race.

During the seventeenth and eighteenth centuries variola was constantly on the increase, only a favored few being spared an attack of the disease. It occurred mostly among children, adults more rarely contracting the disease because of the immunity acquired from the attack during childhood. Children who had not had small-pox were considered "susceptible," and a case of the disease occurring where a number of such susceptibles were gathered was the starting point of epidemics on many occasions. In the larger European centers the scourge appeared in epidemics of more or less severity in periods ranging from four to six years.

Although writers, as late as the sixteenth century, failed to distinguish variola from measles, they seemed to recognize the contagious nature of the disease. During the following centuries (the 17th and 18th) there gradually arose a better scientific understanding of variola, and to Sydenham belongs the distinction of having made the first differentiation of measles and variola. But at the same time he was not so entirely convinced of the contagious nature of variola, rather leaning to the theory that the disorder was a sort of healing process by which the body in a natural way rids itself of harmful secretions. His therapeutic suggestions were entirely opposed to those in vogue at the time. He recommended a cooling, antiphlogistic treatment which would hasten the outbreak of the eruption, allowing his patients to be out of bed in the fresh air until the eruption appeared; if the patient was unable to be up he insisted upon plenty of fresh air for the sick-room.

Another advocate of fresh air was Boerhave (1668-1738), who also advised the use of cathartics, emetics and cupping for the fever. To this physician belongs the credit for the idea of controlling the spread of variola by isolating the patient. Not only was he convinced of the contagious nature of variola, but he observed that it was carried by the air and entered the body through the respiratory tract. Although isolation in those days was neither largely practiced nor carefully carried out, that it afforded a degree of control for the disease is evidenced from the historic example of Rhode Island, whose laws required that all sufferers from small-pox be isolated on the Island of Coasters Harbor, with the result that from 1740 to 1765 no epidemic of small-pox was known

in that State. But, on the whole, quarantining variola victims proved of little avail in the general control of small-pox.

An early German writer jocosely remarks that few escape small-pox and love. This may well be taken to indicate the general resignation with which an attack of small-pox was accepted as one of the inevitable or practically inevitable facts of life. Accordingly, efforts were directed not so much toward controlling the disease as toward devising means of controlling the attack, i.e., making it as mild as possible, and thus gaining immunity for life. The idea of variolation for this purpose is almost as old as the history of variola itself. The method and its evolution into vaccination, as introduced by Jenner, are discussed at pages 191-194. Since Jenner's day small-pox has been decreasing in proportion to the prevalence of the custom of vaccination, thus realizing the vision of Moore, who, in 1815, wrote: "Infectious diseases spring up in obscurity, and extend indefinitely; but if opposed with judgment, they might, like empires, be controlled; and would decline and fall. The small-pox has past through the first stages, and is now sinking into the last."

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CHAPTER X

VACCINIA (*Vaccination*)

BY SAMUEL SIDNEY WOODY, M.D.

Definition, p. 215—Relation of vaccinia to variola, p. 215—Symptomatology, p. 215—Mode of onset and normal course, p. 215—Indications for vaccination, p. 217—Technic of vaccination, p. 217—Revaccination, p. 218—Complications and association with other diseases, p. 218—Treatment, p. 219—Historical summary, p. 219.

Definition.—Vaccinia, or vaccination, is a febrile disease acquired only by inoculation with the virus obtained from cow-pox (bovine virus) or from a human subject who has been inoculated against variola (humanized virus), and producing a number of lesions corresponding to the number of insertions.

Relation of Vaccinia to Variola.—The relation of vaccinia to variola has not yet been definitely explained. The accepted theory is that the virus of small-pox is altered during its passage through one of the lower animals, so that it loses its power of inducing small-pox but retains sufficient antibodies to act as a protection against the disease. The identity of the virus of variola and of vaccinia is established by the presence in both, as well as in skin sections of both diseases, of microscopic cell-inclusion bodies, first described by Guarnieri, in 1892, and later confirmed by Pfeiffer, Councilman and others. The studies of these bodies led these investigators to the conclusion that they are protozoa closely related to the etiology of vaccinia and variola. Fornet has described small diplococci which he found in lesions of both diseases and which he believed to be etiologically related to variola. Confirmation of these findings would establish the identity of the two disorders, but that confirmation has not been forthcoming up to the present.

Copeman, of England, and Tyzzer, in this country, have shown by experiments that vaccination protects the monkey against subsequent inoculation with small-pox virus, thus confirming Jenner's early experiments, which demonstrated the efficiency of vaccination by variolation, or the "variolus test."

Symptomatology.—MODE OF ONSET AND NORMAL COURSE.—The incubation period of typical vaccinia, especially after a primary vaccination, is remarkably constant. For the first three days after the operation there is no local reaction except that due to the trauma of the act of vaccination. At the end of the third day, or the beginning of the fourth day, the site or sites of inoculation reddens, swell into tiny macules

which, within the next twenty-four hours, develop into flattened papules. About the fifth day the pock is surrounded by a small hyperemic areola from which the papule rises like the nipple from the mammary areola. It then changes into a transparent vesicle and reaches complete maturity on the seventh or eighth day, when it presents a full round vesicle with a slight central depression containing a yellowish scab—the tissue from the vaccination scar. On the ninth or tenth day the vesicle becomes pustular and shows definite umbilication. Desiccation then sets in almost at once, the center dries, the crust forms and rapidly grows outward until it covers the entire pustule, falls off (if not disturbed) on the fourteenth to the twenty-fifth day, leaving a reddish scar which in the course of a month or two becomes white and finally leaves a pitted mark.

The reddish areola, widening during the development of the pock and often extending several centimeters beyond it, is one of the most pronounced features of vaccination, and when several such areas develop around three or four sites of inoculation on the same arm, for example, their confluence is apt to be mistaken for erysipelas. But their outlines are much less well defined than those of erysipelatous lesions.

Slight variations from the normal course of vaccinia may sometimes be observed, especially in healthy young children during the hot summer months, or in winter in a heated room, when the pocks develop more rapidly; or in under-nourished children, when apt to develop more slowly. The incubation period may also vary in different pocks on the same individual, some developing more slowly than others. Certain authors have noted a compensatory process in such cases, the slow-growing efflorescences making up by going through the different stages more rapidly, the areola appearing at about the same time in all, and only the papules of the slower ones something lagging. A cachectic reaction is also described as sometimes occurring in anemic children, the areola being indistinct, signs of the same not appearing until the tenth or twelfth day. The papule, however, develops normally. Fever is correspondingly slight or altogether absent.

The *subjective symptoms* comprise intense itching which begins on the third or fourth day after inoculation and is accompanied by more or less severe pain in the arm and perhaps in the axilla, and is again followed by itching during the process of healing. Sometimes on the third or fourth day after the incubation period there is a slight rise in the evening temperature, but as a rule the temperature rises irregularly, reaching its maximum, 101°–104° F. (38.3° to 40° C.), on the eighth day. The pulse, corresponding to the temperature, is more or less rapid, and there may also be general malaise, loss of appetite and of sleep. Adults often complain of headache, languor and sometimes nausea; in children there may be more or less delirium.

Albuminuria during the course of vaccination is very rare, and is then eminently a febrile manifestation. Nephritis is not known.

Among the *anomalies of vaccinia*, due to the inoculation of the vaccine virus elsewhere than at the intended site, are polymorpho-

postvaccinal exanthem and the eruption—accessory pocks, generalized vaccinia—due to transmission by direct transfer or by way of the blood and the lymphatics (auto-inoculation), and accidental inoculation by transfer of the virus, from the individual vaccinated to a second person.

The postvaccinal exanthem is an urticarial, morbilliform or roseola-like rash, the most pronounced feature of which is violent itching. It appears about the seventh to the fourteenth day after vaccination, beginning on the face, and extending downward to the trunk and the extremities. It can be differentiated from *rubella* by the absence of swelling of the cervical glands, and from *measles* by the absence of Koplik's spots and symptoms of coryza. Jochman attributes this to anaphylactic reaction, since two of the twelve children in whom he observed it were immune, the vaccination failing to take.

Accessory or secondary pocks by *auto-inoculation* may arise around the site of vaccination or in any other part of the body. Some authorities claim that they are due to transmission of the virus through the lymphatics, since they usually develop at a time when the primary vesicles begin to fill with lymph. The pocks usually abort, rarely progressing beyond the papular stage. This is explained by the fact that the patient has already developed a partial immunity which, as it becomes complete, prevents the full development of the pocks. In most instances, however, the *secondary inoculation* is an accidental one *through direct transference* of the virus by means of the fingers or through the careless use of towels which have come in contact with the vaccination pustule. Not only can the vaccinated person inoculate himself in this way, but he may also affect another individual. Conjunctival and also nasal vaccination result from such accidental transference of the virus. Such pustules arising on the eye should be treated with the mildest sort of solutions. They generally heal without leaving any effects, although serious eye trouble may follow.

Indications for Vaccination.—The best time for a primary vaccination is early infancy—between the fourth and the sixth month—when both the local and constitutional reactions are apt to be less severe and there is also less danger of secondary infection. The only contra-indication to early vaccination is, of course, the state of the child's health. If the child is delicate or under-nourished, owing to improper assimilation, or in the presence of an eczema or of syphilis, it is better to postpone the operation until the condition is improved. In case of exposure or during an epidemic it is justifiable to vaccinate a child at any time, taking a chance with the contra-indications as the lesser of two evils.

Technic of Vaccination.—The technic of vaccination is a matter of choice. Some governments require four inoculations; some physicians make three and others only one, selecting either the arm or the leg for the purpose. It is our practice to choose the outer surface of the left arm just below the insertion of the deltoid muscle; sometimes, if desired in females, the leg below the knee may be chosen. After thoroughly cleansing the chosen site with soap and water, followed by alcohol, the site is allowed to dry. The virus is then dropped on the cleansed

area, which is then scarified with a blunt lancet, needle or any of the special instruments devised for the purpose. Three or four parallel abrasions $\frac{3}{16}$ inch (4.6 mm.) long are made, penetrating the skin just enough to show serum but not to cause bleeding, the virus all the while being rubbed in cautiously so as to prevent the escape of serum or blood. A temporary **shield** is applied only for the purpose of preventing infection or rubbing off the vaccine by the clothing. It should by all means be removed after twenty-four hours, as its further use would be harmful. The shield is easily made of a circular piece of cardboard, somewhat larger than the inoculated area, slit to the center at one point, turned into a cone and fastened with adhesive plaster. The only other local treatment, except in the event of secondary infection, is painting the site twice daily, beginning two days after the operation, with a solution of **iodin**, 1 part; **picric acid**, 4 parts; and **alcohol**, 95 parts. This lessens the chance of outside infection, cuts short the acute stage of the process and in no manner interferes with its efficacy.

At the present time the manufacture of vaccine lymph is carefully carried out and there is no danger of contamination. This does not lessen but rather increases the responsibility of the physician, since with a lymph of known reliability any accident is directly due to faulty technic; that is to say, lack of proper cleanliness of his hands, sterilization of instruments and dressings. Nor does his duty end with the operation. The patient should be **kept under observation** for indications of possible secondary infection.

Vaccination is without doubt one of the greatest blessings that medical science has given mankind; but there is still considerable opposition to the method, and it is the duty of the medical profession to do nothing that will discredit it in the eyes of the public.

Revaccination.—The protection afforded by a primary vaccination, although it is never entirely nullified, gradually diminishes, so that it is desirable to revaccinate children at the age of seven to ten years and at adolescence, and during adult life as occasion arises through exposure to the risk of contagion, or as a preventive measure during an epidemic. There are no contra-indications to vaccination during an epidemic or after a known exposure to small-pox. In the interest of public health vaccination, if it is not already compulsory, should be insisted upon at every such occasion. If this were practiced everywhere variola would soon disappear from the face of the earth.

The course of revaccination often deviates from that of a primary inoculation. On about the second day there is local reddening and irritability; the papules appear on the third or fourth day and may or may not develop into vesicles and pustules. Very often revaccination fails altogether; in such instances it is advisable to repeat the inoculation with a different virus, if possible, before definitely concluding that the subject is insusceptible.

Complications and Association with Other Diseases.—Vaccination, though it generally runs a perfectly normal and benign course, may be associated with complications, the most important of which are *tetanus*

and *erysipelas*. Neither of these, however, is peculiar to vaccination, since either may result from infection from any skin lesion. And in so far as carelessness in the operation and possible abrasions of the skin lesions of vaccinia—especially in a weakened individual—offer convenient portals of entry for all kinds of bacteria, it might be said that vaccinia may be associated with any of the various types of infection. Some anti-vaccinationists claim that *syphilis*, *tuberculosis* and *leprosy* may be acquired through inoculation with the vaccine virus. The use of glycerinated calf lymph should in all instances absolutely prevent any such occurrence, since experiments show that neither the tubercle bacillus nor the streptococcus of *erysipelas* are able to survive prolonged exposure to the action of 50 per cent. solution of glycerin in water; and, furthermore, the calf does not acquire either syphilis or leprosy.

The normal course of vaccination may also be complicated by an intercurrent acute infection, such as *measles*, *scarlet fever*, *whooping-cough*, *varicella*, *influenza*, without, however, affecting either the vaccinia or the superadded infection. The one exception to this ruling may possibly be *diphtheria*, where prognosis is sometimes unfavorably affected when it accompanies vaccinia.

As to the question of vaccinating a patient already suffering from one of the acute infections, it is our feeling that these patients have all they can do to throw off the illness from which they are suffering and that if at all possible vaccination should be postponed until recovery has taken place. This is particularly true of *scarlatina*, where the skin is already devitalized and the air of a scarlet fever ward is charged with organisms—especially streptococci. Under these conditions secondary infection is liable to occur. We believe that nothing should be done that may prejudice the public against so eminently a beneficent procedure as vaccination and, we repeat, unless absolutely imperative it should not be done under adverse conditions.

Treatment.—Little is required in the way of general treatment of vaccination, except during the *febrile stage*, especially in young children, when **rest in bed**, **light diet** and **attention to the bowels** are indicated. A **fever mixture** may be given, if necessary, but ordinarily little more will be needed. Any marked constitutional symptoms should suggest secondary infection, the treatment of which is the same as for any wound infection after abrasions or other injuries to the skin.

Historical Summary.—The precursors of Jenner's protective prophylaxis against variola date back to ancient and medieval times. The observation, that individuals who had recovered from small-pox never suffered a second attack, led to the supposition that the artificial production of a mild form of the disease (variola) might have the same result. The most primitive type of such variolation is that practiced by the Chinese, who mixed the crusts of variola pustules with musk, wrapped them in cotton, and after they had been kept for years and treated with vapors of all kinds and with medicinal herbs in order to attenuate their virulence, were inserted into the nostril of the person to be protected. It was also customary for the individual to don a shirt

which had been smeared on its inner surface with the pus of the variola pustules.

Somewhat more logical was the Brahmin manner of variolation practiced in India. This consisted in introducing the material from a variola sore into the skin on the upper arm by means of a needle, making fifteen or sixteen scarifications and covering the scarified area with a tuft of cotton which had been dipped in variola material, and sprinkling it with holy water from the Ganges River. The pock material used was always at least one year old and was taken from an inoculated individual, not from a case of spontaneous small-pox. The patient was obliged to remain in the open air and to avoid intercourse with his fellowmen, and to restrict his diet to fruits, rice and light food.

Needle puncture was also the method used in other oriental countries—Persia, Armenia, Circassia, Georgia, etc. The Circassians and Georgians, in order to make sure of results, used three needles tied together and pricked the body in several different places when introducing the variolous material. In all these countries the practice was called "buying the small-pox," the origin of which is supposed to be the custom of giving the child to be inoculated a few raisins, dates or sweets to carry in his hand and, showing them to the child from whom the material is to be taken, asking how many pocks he will give in exchange for the sweetmeats. This practice spread among the common people along the coast of Africa and even passed over into European countries, Italy, France, Germany, Sweden, Denmark and South Wales.

The first accounts of the oriental mode of variolation came to Europe through the writings of a Greek physician, Timoni. This consisted in inoculating the fluid contents of variola vesicles into the arm of the recipient through a needle puncture which produced a mild form of the disease with pustules scattered over the body. The impulse to the use of the method was given by Lady Wortley Montagu, the wife of the English Ambassador to Constantinople, who, in letters to friends, enthusiastically described the procedure and advocated its use after her two children had been successfully treated. This mode of variolation, however, fell far short of the ideal one, for it not only produced the disease with most of its serious features, but also provided a means of spreading contagion which not infrequently proved to be the starting point of an epidemic.

It was reserved for Edward Jenner, a simple country doctor, to present to a waiting world the ideal prophylaxis against small-pox, which represents one of the signal triumphs of preventive medicine, the benefits of which it is impossible to over-estimate.

For a long time it was a well-known fact that cow-pox, formerly much more common during pandemics of variola than at present, was transferable not only from one animal to another but also to man. Dairy hands became infected from the udders of cows through slight abrasions or excoriations on the skin of the hands, where they developed small vesicles which, after progressing into pustules, dried up. Similar lesions arose at other sites on the body, but only if transferred from the original

one by means of the fingers. The disease, however, was purely a local one unaccompanied by any general exanthem.

Long before Jenner's time it had been generally observed that persons recovered from cow-pox were subsequently immune to true variola. Jenner, the son of an English clergyman in Berkeley, England, while a student of medicine in 1768, overheard a milkmaid say that she could not get small-pox because she had had cow-pox. The remark made a deep impression on the young student, who from that time continually occupied himself with the relationship of cow-pox and variola. During a period of over twenty years Jenner collected and correlated all existing observations and experiments on prophylaxis of small-pox and, by means of personal experiments, endeavored to solve the question. He began by inoculating sixteen individuals, who at a more or less remote period had had cow-pox, with the lymph from genuine variola, and in all cases he failed to obtain variolation—the inoculated individuals all being immune. His next step was a decisive one and entirely original in the annals of medicine. On May 14, 1796, Jenner inoculated an eight-year-old boy, named James Phipps, with the lymph of cow-pox taken from the hand of a milk-maid, Sarah Nelmes, thus establishing the first instance of inoculation with human lymph. The result was typical cow-pox in the boy. Jenner then resorted to the crucial test of inoculating the same boy with the lymph of genuine variola, which, according to his expectations, proved negative, i.e., variola did not develop. The first test, made on July 1, 1796, was followed a few months later by a second one, with a similar negative result. He was thus enabled to demonstrate for the first time that the lymph of cow-pox is transferable not only from the cow to man, but also from man to man, and that the transference of humanized vaccine confers the same protection against variola as the natural lymph of cow-pox. It was not, however, until after repeated successful experiments that Jenner finally, in 1798, published the results of his epoch-making discovery. The benefits of vaccination have since accrued to mankind everywhere, for vaccination is practiced to-day in virtually all civilized communities, and, in most localities where it is not compulsory, it is at least a prerequisite for admission to schools, institutions and to some business houses.

Vaccination was introduced into the United States during the year 1800. In July of that year Dr. Benjamin Waterhouse, Professor of Physics at Harvard University, vaccinated his own children, and at about the same time Dr. John Redman Coxe, of Philadelphia, vaccinated his oldest son, and in order to test the experiment boldly exposed him to small-pox contagion. The exhibition of the child's total immunity did much to establish confidence in Jenner's method and to introduce it throughout the country.

That Jenner and his supporters should have been subjected to much unpleasant criticism and opposition is not surprising, but that there should still be those who systematically oppose the practice seems incredible in this twentieth century, when the boon of this discovery has become apparent in the waning and in the possibility of the ultimate eradica-

tion of variola from the arena of medicine, though unfortunately it is too true. Councilman has well described this peculiar type of individual who makes up the antivaccinist: "Small-pox can, but probably never will be wholly eradicated. The chief obstacle which stands in the way of its eradication is an inability to recognize facts, and to make the proper deductions from them, which seems to be associated with certain orders of mind. The facts with regard to the production of small-pox immunity by vaccinia are perfectly established. The order of mind which leads to their denial will probably never disappear from the human race."

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CHAPTER XI

VARICELLA (*Chicken-pox*)

BY SAMUEL SIDNEY WOODY, M.D.

Definition, p. 223—Etiology, p. 223—Symptomatology, p. 224—Diagnosis, p. 225—Differential diagnosis, p. 225—Complications, p. 226—Sequelæ, p. 227—Association with other diseases, p. 227—Clinical varieties, p. 228—Treatment, p. 228—Prophylaxis, p. 228—General management, p. 229—Management of convalescence, p. 230—Prognosis, p. 230—Pathology, p. 230—Historical summary, p. 231.

Definition.—Varicella or chicken-pox is a highly communicable, mildly acute, exanthematous disease, characterized by a long incubation period, feverishness and a vesicular eruption appearing in crops and drying up in a few days with or without leaving pitted marks.

Etiology.—The disease is disseminated over the entire world, is endemic in large cities, epidemic at times, but generally considered to be more prevalent in the autumn months. It is eminently a disorder of childhood with no discrimination with regard to race, and little, if any, as to sex. Adults, however, are not entirely immune, as many as six per cent. in a series are reported to occur after puberty. We have observed it in a man 64 years of age; others report their oldest case at the fiftieth year. It is rarely seen before the sixth month after birth, although instances are recorded of new-born infants developing varicella as early as the eleventh to the fourteenth day, having been infected from the mother. The period of greatest susceptibility occurs between the fourth and the tenth year of life.

The virus of varicella is not known, nor is the mode of communication definitely established. Experience indicates that it can be transmitted by a third party and also by aerial convection. Indeed, we find that it is the one disease that can be communicated from ward to ward in a hospital and even from building to building, in spite of the most painstaking efforts to prevent its spread. It is transferable from the moment of onset of an attack, but unlike the virus of variola, the varicella virus is short-lived, so that infection by fomites is more or less doubtful.

Tyzzar, in a study of the histology of the skin lesions of varicella, observed certain inclusion bodies in the cell-nuclei and the cytoplasm, which he was inclined to think specific, but failure to produce new lesions by inoculation with the bodies forced him to conclude that they were not parasitic. Keyssellitz and Mayer also observed similar bodies which they believed analogous to cytoryctes, and, although non-parasitic, contained the infective virus.

Symptomatology.—The varicella eruption usually appears on the fourteenth day after exposure to the disease, but it has been known to develop as early as the eleventh day. In our experience the *incubation period* has been prolonged to the twenty-second day, while some authorities report an incubation period of thirty days after a known contact.

Prodromal symptoms are often entirely wanting and when present are slight, the eruption (especially among private patients) being generally the first sign of the disease. Observations in the scarlet fever and diphtheria wards of a fever hospital usually show that more or less fever precedes the eruption by several hours or even a day or two. The temperature may go as high as 104°–105° F. (40°–40.6° C.) and may be accompanied by depression, languor, loss of appetite and nocturnal restlessness. Exceptionally the early symptoms are more aggressive, extending over a period of four or five days, accompanied by malaise, backache, abdominal pain, vomiting, epistaxis. But marked symptoms do not presage a severe attack and vice versa. In the adult the prodromal symptoms are apt to be severe and prolonged, quite often simulating those of variola and confusing the diagnosis.

Some authors describe an urticarial, a morbilliform or a scarlatini-form rash. Our experience is confined entirely to the scarlatinal prodromal rash. The eruption is apt to be punctate, often so closely resembling that of true scarlet fever as to send the patient to the scarlet fever ward, only to have the varicella eruption develop a few hours later. Other cases suggest a scarlatino-varicella infection and prove to be varicella. The rash produces no general symptoms although, according to some writers, it is accompanied by burning sensations, headache, dizziness, joint pains and slight difficulty in swallowing. It generally disappears in about twenty-four hours.

The eruption usually begins on the covered parts of the body, the back, sometimes the scalp, and spreads to the face, the rest of the trunk, and the extremities, preferably their proximal portions; not infrequently it also attacks the mucous membrane of the mouth, the pharynx, the larynx and that of the genitalia.

At first the efflorescences appear as small pink spots which soon become papular and vesicular; but often they abort and never develop beyond the first or second stage. The eruption appears in successive crops, so that efflorescences can be observed at the same time in all stages of development from the macular to the desiccating scab stage. The vesicles are thin-roofed and rupture easily on pressure. They may vary in number from ten to several hundred or thousand; in size they may range from that of a pin-head to a diameter of 10 mm., the average being that of a pea; pemphigus-like sores as large as a silver dollar have also been observed. The vesicles at first contain a clear fluid which becomes pearly and turbid just before they begin to dry up. Sometimes an irregular reddish areola develops around the base of the vesicles, giving them the appearance of variola lesions. Very often, especially in undernourished children, the vesicular contents becomes purulent, secondary infection of which may lead to ulceration persisting for several weeks.

The eruption runs a mild course, the vesicles beginning to dry up in a day or two. But owing to the fact that they develop in crops, the desiccation process is generally prolonged over five or six days; in fact, two to three weeks is often required for the completion of the entire process. The crusts that form are shed and leave a reddish-brown stain, or in some instances a tiny umbilication from destruction of the true skin.

Even in the mildest sort of case the varicella eruption may attack the mucous membrane of the mouth, the hard palate, the tongue, the gums, as well as the tonsils and the pharynx, and also the external genitalia. As a rule, the only discomfort caused by the spots in the mouth and throat is a little difficulty in swallowing or in masticating. Inflammatory infiltration, however, may lead to secondary stomatitis, burning sensation in the throat, tonsillitis with general symptoms including orchitis (in the male). Perforation of the soft palate from an ulcerating varicella lesion has been reported. Occasionally the eruption involves the larynx and gives rise to croup-like symptoms (croupous varicella) which may require intubation or tracheotomy. When inspection of the larynx is not possible in such cases and diphtheria cannot be definitely excluded, it is well to be on the safe side and administer diphtheria antitoxin.

The *temperature* even when it has been high during the period of invasion generally falls to the normal in the course of one to three days. In rare instances fever may persist five or six days, and in small children may be marked and accompanied by a very profuse eruption. Secondary infection of varicella lesions may prolong the febrile period for two or three weeks.

After the eruption is well established there are practically no constitutional symptoms except perhaps itching, caused by contact of the skin with the clothing.

Diagnosis.—The diagnosis of the typical case of varicella presents little difficulty. The long incubation period, the absence or mildness of the prodromal symptoms, the appearance of the eruption in crops and the moderate fever are the common features of the disorder. In certain instances, however, it is difficult, if not impossible, to differentiate.

DIFFERENTIAL DIAGNOSIS.—*Variola.*—The one condition of importance with which border-line cases may be confused is variola, especially in its milder form or when modified by more or less remote vaccination and when occurring in the adult. The importance of arriving at a positive diagnosis is readily apparent. Failure to do so may result disastrously to the community in general and to the attending physician in particular. A history and evidence of successful vaccination in a child, and vaccination within a period of six or seven years in the adult would ordinarily speak in favor of varicella. In the absence of such a history it should be remembered that variola is generally preceded by a three days' prodromal stage accompanied by high fever and severe backache, and that the eruption begins, preferably, on the exposed surfaces, the face, the arms, the back, the lower extremities, especially the distal portions. It is also generally more abundant on the shoulders than over

the loins and more profuse on the chest than on the abdomen, while the varicella eruption shows no such constant differences. In variola the density of the eruption increases from above downward (centrifugal distribution), while the density of the varicella rash increases from below upward (centripetal distribution). The lesions of variola lie deep among the epidermal cells, while the lesions of varicella are superficial. The variola lesions at first present firm papules which increase slowly in size and develop into vesicles and pustules. They are circular in outline, while the varicella lesions are oval, jagged and irregular, are never actually indented and are soft and velvety to the touch. The variola lesions, on the other hand, are frequently indented and are tense and firm.

Impetigo.—In the desiccating stage the differentiation between *impetigo* and varicella may have to be made. Usually the presence of varicella lesions in the vesicular stage settles the doubt. The pustules and crusts of impetigo are usually more profuse on the face than elsewhere, while the lesions of varicella, even if profuse on the face, are oval in outline. However, it may happen that all the lesions have developed beyond the vesicular stage and owing to the crusts having formed and reformed several times they will have lost their oval shape. In such instances differentiation would be almost impossible and it is well to entertain the suspicion of impetigo and isolate the patient.

Pemphigus.—Early pemphigus where the bullæ are small may possibly be mistaken for varicella, but, as a rule, the large sores appear promptly and clinch the diagnosis.

Complications.—In so benign a disorder as varicella, complications are not likely to occur, although they are not excluded. When they do take place they are generally associated with the skin lesions, any abrasions of which present favorable avenues for the entrance of all kinds of bacteria—pyogenic and others. The most important of such complications is erysipelas, which may develop about the efflorescences—especially the deep-seated ones—and may be so severe as to cause death. In neglected cases especially, an impetigous inflammation on the scalp may result from scratching a vesicle and, owing to the want of cleanliness, lead to local eczema. In rare cases a gangrenous dermatitis—often considered a variety of the disease but in reality a complication—may result from ulceration of infected vesicles, especially those at or near the external genitalia.

A varicella vesicle on the eyelid may lead to severe conjunctivitis, but usually it provokes only a marked edema. Very occasionally the eruption involves the cornea, producing ulceration and opacity, or more deep-seated lesions, may result in panophthalmia and destruction of the eye.

Simple and suppurative adenitis have been reported while nephritis, though not common, is a sufficiently frequent complication of varicella to warrant careful management to prevent its occurrence. It may complicate the mild as well as the more serious cases, and usually appears on the eighth to the fourteenth day of the disease. In pronounced cases

the nephritis may be associated with fever, albuminuria and all the severe manifestations of true scarlatinal nephritis. The prognosis, however, is favorable, as it usually subsides in about two weeks' time and leaves no permanent effects. Arthritis, synovitis, disturbances of the central nervous system—myelitis, encephalitis, otitis media—are sometimes mentioned as complicating varicella, but they are exceptional. Gastro-intestinal disorders—particularly appendicitis—are also reported as complicating the disease, but by the majority of the profession they are regarded as incidental phenomena.

Pulmonary complications—bronchitis, bronchopneumonia—occasionally develop during an attack of varicella, especially when it enters as a cross-infection in whooping-cough or measles.

Sequelæ.—It is only natural that a benign disease that presents few complications should be equally devoid of sequelæ. Jochmann mentions the influence of varicella in arousing latent tubercular conditions, especially of the glands or the lungs, and the possibility of the development of miliary tuberculosis. But such instances are as rare as any other sequelæ of varicella.

There is an impression that the varicella patient shows a particular susceptibility to scarlet fever, due, no doubt, to the possibility of an abraded varicella vesicle as the avenue for the scarlatinal infection. On the other hand, the presence of any of the infectious diseases, such as scarlatina, measles, whooping-cough and others, does not affect the susceptibility to varicella, but the weakened condition of the patient may influence the course of the superadded disease and lead to suppuration and ulcerative degeneration of the varicella efflorescences.

Association with Other Diseases.—A question that has of late been receiving considerable attention is the relationship between varicella and herpes zoster. The association of the two diseases was first pointed out by Bokáy in 1892, who, several years later, reported nine observations. Le Feuvre, in 1914, had collected thirty-eight reports, including several personal observations, many concerning several instances seen by one and the same author. Other observations have been recorded from time to time, among them the 3 cases recently reported by Goldberg and Francis, and 3 by Low, the total number being now well over 50 (Low). In the majority the varicella eruption develops without any other demonstrable source of contagion than an existing case of herpes zoster; in others the herpes follows after the varicella, the latter infecting contacts after the usual incubation period; and in some few the herpes is followed in the same individual by a varicella eruption. For this aberrant eruption (of herpes) Le Feuvre suggests the name *varicella herpetica*. Low is strongly inclined to the conclusion that the two diseases are due to the same virus, which may belong to the ultramicroscopic filterable group of organisms. He suggests that in herpes, infection is probably local through the nose, that is, the lymphatics around the olfactory nerves, similar to that of epidemic poliomyelitis, with which it has many points of analogy. The virus after reaching the meninges and the cerebrospinal fluid easily gets to the ganglia of the sensory nerve trunks. In varicella there is a blood

infection with the virus, and in those cases which simultaneously present the two eruptions, the virus probably first attacks the ganglia and then, three or four days later, gets into the blood and produces a general eruption.

The question of *immunity* is interesting in this connection. One attack of varicella conveys immunity for life, second-attacks being most unusual, if at all possible. If herpes zoster and varicella are due to the same infectious agent it would be reasonable to suppose that an attack of one disease would provide immunity against the other. According to Low, however, it appears that herpes zoster protects against varicella, but varicella does not protect against herpes. Adults that have had varicella in childhood develop herpes, but he finds no instance of a case of herpes which developed varicella later on, and in no case of herpes associated with a generalized varicella eruption was there a history of a previous attack of varicella.

Clinical Varieties.—The clinical varieties of varicella, like the complications, also concern variations in the skin lesions. In addition to *gangrenous* dermatitis (already mentioned) the eruption may be *confluent*, and *hemorrhagic*. Confluent varicella is rare. The lesions may be multilocular, and the skin edematous, and fever may supervene if pustulation takes place. The hemorrhagic type is also not common. Hemorrhage, either purpuric or petechial, may take place into the skin and subcutaneous tissues, or the efflorescences may become hemorrhagic, with discoloration of the skin due to extravasated blood; hemorrhage may also take place from the affected membranes. Hematuria has also been noted.

Treatment.—**PROPHYLAXIS.**—**Isolation** of the patient is *neither imperative nor really practical*. The disease is a benign one and is not worth the inconvenience which, owing to its highly communicable character even in its earliest stage, would be required to make quarantine effective. Contacts need not be detained for more than three weeks; infection so rarely occurs later, that longer detention is unjustifiable. To prevent unnecessary loss of time at school contacts may be permitted to attend school for ten days following the first exposure. They should then be kept at home until there seems no danger of developing the disease. Prophylactic **vaccination** has been attempted with varying degrees of success by Kling, Handrick, Rabinoff, Rutelli, Hess and others. Kling (in the service of Medin of Stockholm), although not the first to make the attempt, was the first to report results in a considerable number of cases. During an epidemic (1913) in an orphan asylum he inoculated 58 children with lymph from a clear varicella vesicle collected on a lancet and rubbed into a scarified area on the arm; only 1 of the children developed chicken-pox; 31 showed lesions at the site of inoculation, consisting of red papules which rapidly developed into typical vesicles and dried up in two or three days; 6 children developed papules with occasional vesicles. Of 64 children that were not vaccinated 44 developed varicella.

Rutelli as well as Rabinoff report similar success. The latter ob-

served an incidence of 6 to 8 per cent. among vaccinated, against 75 per cent. among unvaccinated children, inmates of an orphan asylum and all subject to the same conditions of exposure. She furthermore noted that in those that developed the disease although its course was not affected by the inoculation, the incubation period was shorter than usual and that, contrary to previous experiences in eight other epidemics, no second outbreak of the disease took place. Handrick, on the other hand, observed the disease develop in 35 per cent. of 127 children inoculated, so that he is inclined to doubt the value of the method. In only 3 instances did he obtain a local reaction at the site of inoculation which, however, did not prevent the development of a generalized eruption.

Kling makes his inoculation through a small puncture. Rabinoff makes several small scarifications. Handrick used both Kling's method as well as the method of von Pirquet in giving the tuberculin test. Rutelli made the inoculation on a scarified area on the abdomen and obtained marked local reaction in all the 15 cases, one infant developing a small abscess on the twentieth day. Hess, on the other hand, finds these simpler methods less satisfactory than the intravenous injection of a solution of the fluid from a varicella vesicle in normal saline. Of 38 children thus immunized only one developed the disease and that 36 days after the injection. No general reaction is reported by any of the authors.

GENERAL MANAGEMENT.—Very little is required in the treatment of varicella except **rest in bed** until the lesions are well past the acute stage. In the presence of fever the **diet** should be light and, if necessary, a **fever mixture** may be prescribed.

The general treatment of varicella is purely **symptomatic**. The patient should be **kept in bed** until the crusts have fully formed and until the temperature has been normal for several days and examination of the urine proves it to be negative. The only real danger of varicella is secondary infection through the lesions. To avoid this, **cleanliness** is important. The patient's hands, especially the finger-nails, must be kept clean and the latter closely trimmed, and should be tied in padded mittens or stockings. It may at times be necessary to prevent scratching by restraining the arms and legs. *Itching* can be controlled by means of **tepid baths** or by **sponging** with alcohol well diluted with water or vinegar water, three parts to one, followed by a **dusting powder** consisting of the following:

R

Mentholis	3 ss (2 grams)
Zinci oxidi	3 i (4 grams)
Pulv. amyli	3 i (32 grams)
Talci	3 i (32 grams)

Should *secondary infection* occur the usual local and constitutional treatment must be instituted. Thick infected scabs or crusts should be softened and removed by **applications of olive oil or poultices**.

For the resulting ulcer an ointment of ammoniated mercury may be employed, or better still, an evaporating lotion as follows:

R	
Pulv. calaminæ	℥ ii (8 grams)
Zinci oxidi	℥ ss (16 grams)
Glycerini	℥ i (32 grams)
Liquor calcis	f ℥ ii (60 c.c.)
Aquæ rosæ	f ℥ viii (240 c.c.)

Gangrenous dermatitis should be treated by supportive measures, such as **fresh air and liberal feeding**; tonics, cod-liver oil and malt, and **stimulants** may also be required. For the local treatment of the gangrenous skin lesions we advise that only the **blandest kind of solution** be used; strong solutions we believe are contra-indicated.

The mouth lesions are treated by any of the **bland mouth washes**. Ulcerations will require suitable treatment, such as recommended for ulcerative mouth conditions of scarlet fever.

Special attention should be paid to **general cleanliness**. The **bed-clothing and underwear** should be changed frequently. The patient should be given a **daily sponge bath**, and particular care taken to keeping all lesions, especially those on the external genitalia, clean.

MANAGEMENT OF CONVALESCENCE.—The patient may be considered cured when the separation of the scabs is complete. In the average case, where there is no secondary infection, about three weeks' time will be required for the process. Any crusts that have reformed need not be considered infectious. In such instances it is necessary only to **remove the crusts and carefully cleanse the resulting ulcer**, by touching it up with a **reliable antiseptic solution**.

Prognosis.—The prognosis of varicella is altogether favorable and is not affected by complications such as nephritis, laryngitis or secondary pyogenic infection, should they occur. The bright outlook is marred only when the varicella appears as a superadded infection in a patient already weakened by previous disease—whooping-cough, measles, scarlatina, diphtheria. In such circumstances the varicella is apt to develop seriously and the resulting sepsis may lead to gangrenous dermatitis, pulmonary disease, etc., which often threaten life, and in about five per cent. of cases of such cross-infections are the actual cause of death.

Pathology.—The pathology of varicella is practically limited to the skin lesions. Unna has described the conical lesions as having a tent-like form with lateral walls rising obliquely from a broad base towards the center of the covering composed of a few horny stretched scales. From this covering cellular septa radiate downwards, in contrast to the lesions of variola where the cellular partitions radiate from a central point on the floor of the lesion. In varicella the cavity proper is limited below by the deeper strata of the prickly layer which shows pathological changes. In the center the cavity extends deeper to the level of the swollen and enlarged papillæ which are covered with one or two layers of modified epithelium and project into the cavity. The acute character

of the eruption in varicella is evidenced by the comparatively slight septate cavities due to the rapid distention of a few liquefied cells. The rapid formation of the vesicles which are unilocular, accounts for their thin roof and superficial position.

The latter together with the absence of suppuration and the early repair of young epithelial cells explains the absence of general scarring after a varicella eruption.

Historical Summary.—The first definite description of varicella is that given by Vidus Vidius (about 1626), who also gave it the designation *crystalli*, or *variola crystallinae*, or *ravaglione*, the term still retained by the Italians. It is supposed at that time to have been differentiated from *variola*, but the evidence is doubtful. Morton (1694), who refers to it as *variola admodum benigna*, and his contemporaries regarded it as a mild type of *variola*, a theory which prevailed until Fuller (1730) demonstrated the distinct character of the disease. This duality of the two diseases was generally accepted until toward the middle of the nineteenth century Hebra, one of the foremost dermatologists of his time, revived the 'unity' theory of varicella and *variola*. On account of his eminent position he found many adherents, and it was not until the virulent and widespread epidemic of *variola* during the years 1871 to 1874 that the question of the dual character of the two disorders was definitely settled and universally accepted.

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CHAPTER XII

SCARLET FEVER

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Definition, p. 233—Etiology, p. 233—Predisposing causes, p. 233—Exciting cause: The organism, p. 234—Symptomatology, p. 240—Clinical history, p. 240—Laboratory findings, p. 243—Diagnosis, p. 243—Complications and sequelæ, p. 246—Relapses, recurrences and second attacks, p. 250—Association with other diseases, p. 251—Clinical varieties, p. 252—Treatment, p. 254—Prophylaxis, p. 255—Dick test, p. 256—Immunity, p. 256—General management, p. 261—Serum therapy, p. 269—Prognosis, p. 272—Pathology, p. 272—Historical summary, p. 276.

Definition.—Scarlet fever is an acute, contagious, self-limited disease characterized by sudden onset, a pharyngeal inflammation of varying degrees of intensity, a diffuse scarlet eruption, and desquamation in scales, shreds or casts.

Etiology.—The specific cause of scarlet fever until recently was a matter of conjecture. But in every instance it was known to be dependent upon infection, by contact or otherwise, from a preëxisting case of the disease. Recent investigations, however, have established that the disease is the result of combined toxic and bacterial infection, the specific organism of which is the *Streptococcus hemolyticus*.

PREDISPOSING CAUSES.—*Climate.*—Scarlet fever occurs in all parts of the world, although zones of immunity are known to exist. According to Minor, to whom we are indebted for much of our information with regard to the distribution of scarlet fever, such zones are found for the most part near the tropics, where the high temperature combined with periods of great humidity are unfavorable to the development of a tendency to scarlet fever. In this country such a zone of comparative immunity is located between the 30° and 35° latitude North, comprising the states of South Carolina, Georgia, Alabama, Mississippi, Louisiana, Texas. In general epidemics, however, the disease occurs at all points within these zones.

Season—Altitude.—The effects of seasonal influences vary in different regions. In the countries of Western Europe most epidemics occur during the autumn months, while in the United States the late winter and early spring months seem to be the favored ones. The same holds true with regard to the seasonal mortality statistics. Minor also points out that high altitudes are more favorable to the development of a scarlatinal tendency than low ones.

Sex.—Sex does not play a great part in the etiology of scarlet fever, although the male, especially after the tenth year of life, seems to be slightly more susceptible than the female sex.

Age.—As to age, the tendency to scarlet fever is small at the extremes of life. Infants are rarely affected and individuals after the sixth decade are also generally immune, although scarlet fever among the aged is not unknown. The disease occurs preferably between the third and the tenth years, the curve reaching its apex at about the fifth year of life, with a gradual descent until the fifteenth year is reached and a decided decline after that.

Race.—There seems to be a certain correspondence between the zones

of comparative immunity to scarlet fever and the racial immunity to the disease. Negroes and dark-skinned races are decidedly less liable to it than the white race. In the United States this immunity is six times greater among the negro than among the white population, *i.e.*, six times as many whites as negroes contract the disease. The death rate shows the same relative proportion between the two races. The number of return cases are also relatively less.

Heredity.—There is no evidence of heredity in the incidence of scarlet fever, but there is no doubt of the existence of a personal disposition to it. In rare instances such a disposition takes on a familial character. Welch and Schamberg report two personal observations of family epidemics and cite a number of instances from the literature. On the other hand, there is also a familial immunity to the disease.

Individual Susceptibility.—The individual susceptibility to scarlet fever, however, is not so general as for some of the other infectious diseases—variola and measles, for example. The classic instance of the epidemic of scarlet fever, in 1872, on the Faroë Islands, where no case of the disease had been known for sixty years, presented a favorable opportunity for estimating the general susceptibility to scarlet fever. In this practically virgin soil for the disease 78 per cent. of all the population developed scarlet fever, while in the same islands, in 1875, during an epidemic of measles, 99 per cent. of the population were affected.

Holt believes that not more than half the children exposed contract the disease. He quotes Billington's observation among families occupying tenements in New York, where little or no attempt was made to isolate the cases. Forty-three children were down with scarlet fever, while forty-six other children who had never had it and were constantly exposed to infection did not develop the disease.

Social Conditions.—As to social conditions, scarlet fever is not a class disease except in so far as crowded, unsanitary living conditions and poverty affect the predisposition to disease in general. Since the population subjected to such unfavorable environment is largely composed of the immigrant class, it is not surprising to find a proportionately greater incidence among the newcomers than among the native-born population or among the more prosperous classes.

The more intimate association of children housed in child-caring institutions naturally creates a favorable atmosphere for epidemics which, however, should and can easily be limited to such institutions.

Skin Lesions.—The rôle of skin lesions, especially burns, in the etiology of scarlet fever is practically the same as that of trauma in surgical and puerperal scarlet fever (*see* p. 254,) where direct infection takes place through the open wound. That the broken epidermis undoubtedly serves as a favorable avenue for the invasion of the scarlatinal virus is amply demonstrated by the observation that the exanthem in such cases develops and spreads from the site of the wound.

(The association of scarlet fever with other acute infections is discussed on p. 251.)

EXCITING CAUSE.—*Bacteriology: The Organism.*—In spite of persistent and diligent research the specific inciter of scarlet fever was not found until very recently. Although a full discussion of these investigations is not in place in a work of this kind, it may be of interest to outline

some of the more prominent studies of the question. With the discovery by Mallory (1904) of protozoön-like bodies in the skin layers of scarlet fever patients, it seemed as though the elusive agent were about to be definitely identified. Although the presence of these bodies was confirmed by many investigators, they did not prove specific. Döhle, in 1911, described certain bodies which he observed in the polymorphonuclear leukocytes of the blood from patients in the early stages of scarlet fever. These "inclusion bodies" he supposed to be in some way related to streptococcic infection. Their presence in the early stages is generally admitted. Kolmer found them in 94 per cent. of cases examined, but he also observed that after the sixth day their number decreased and they finally disappeared. Their specificity was, however, questionable, since they were also present in the early stage of diphtheria as well as in other acute infections, such as erysipelas, puerperal sepsis, pneumonia.

The lack of animals suitable for experimentation had undoubtedly hampered the search for the scarlatinal organism, the monkey being the only animal in which a disease resembling scarlatina had been obtained. Among such experiments may be mentioned those of Mair, who (1915) produced a scarlatiniform disease in the monkey from a diplococcus isolated from the throat of scarlet fever patients. The typical rash failed to appear, but the inclusion bodies were present in the polymorphonuclear leukocytes. This *Diplococcus scarlatinae* was subsequently demonstrated by Mair in the first week of the disease in 87 per cent. (of 63 cases) of scarlet fever patients. The organism disappeared, as a rule, about the fifth week of convalescence, the time in the disease at which the patient first ceases to be infectious. Like the mysterious scarlatinal organism, the diplococcus produced profound toxemia which readily yielded to the invasion of other cocci into the blood. There was no evidence that the diplococcus entered the blood-stream in man to any appreciable extent; it appeared to be confined to the region of primary invasion, i.e., usually the throat. Another striking feature of this experimental scarlet fever was that it was complicated by rheumatism; nephritis, however, was not known to accompany the disease in the monkey. The absence of the typical rash did not necessarily exclude the possibility of the diplococcus as the causative agent of scarlet fever. Mair believed that when the actual factor once became known this criterion of scarlet fever would undergo a change since undoubtedly a much greater percentage of cases fail to present the rash than is generally supposed. He also presented an interesting observation with regard to mice as scarlet fever carriers. When mice die as the result of being fed with cultures of the diplococcus, or from the infection itself, the diplococcus can be recovered from the blood. This applies also to wild mice, and might have had an important bearing on the epidemiology of the disease, had the diplococcus proven to be specifically scarlatinal.

Mallory and Medlar in 1916 isolated a Gram-positive bacillus (*Bacillus scarlatinae*) from the tissues of (two) patients dying of scarlet fever. This bacillus seemed to be less virulent than the diphtheria bacillus but was found to invade the same localities, and in severe cases it invaded the adjoining structures, especially the larynx, trachea and lungs. The toxin caused necrosis and destruction of the epithelial covering, thus leading to serous and polymorphonuclear exudates. The primary gross

lesions were inconspicuous on account of the absence of fibrin and of membranous formation, except in cases of secondary streptococcic infection. In six instances, in smears from the tonsils and the soft palate, they obtained cultures of a bacillus whose morphology and staining reaction resembled that found postmortem in the tissues. After death, in severe uncomplicated cases, they found this agent in large numbers in the lesions in the respiratory tract; but in the milder cases it seemed to die out quickly and was not easily demonstrated on the second or third day after the eruption appeared. It seemed, however, to persist for several weeks in the ulcerations in the tonsils, pharynx, larynx, esophagus, bronchi, so that patients harboring it might have become scarlet fever carriers. At the same time the authors pointed out that the study of immune reactions was not positive; that the toxin could not be demonstrated from experiments with culture filtrates on human beings and on animals, although they believed "that it is entirely possible that the organism in tissues and smears has not been obtained in culture, as so far there is nothing but morphology to aid in its isolation."

Pryer and Sewell in 1918 isolated a large organism, with a tendency to be Gram-negative, from the blood of a fatal case of scarlet fever, which they believed deserved serious consideration as "a possible and probable cause of the disease." The organism seemed to be the same as that described by Cantacuzène (1911), who isolated it from the throats of scarlet fever patients and, inoculating monkeys with it, produced a condition resembling scarlet fever. From cultures they prepared a substance which they call scarlatin (analogous to typhoidin from the typhoid bacillus), and using it as a skin test for immunity, found that it gave a higher percentage of reactions in scarlet fever convalescents than in other infectious diseases. They also observed that the probability of a positive reaction increased with the duration of the disease and in the absence of a history of scarlatina the probability of a positive reaction increased with the age of the person tested.

Bacillus streptococcus as the causative factor of scarlet fever has played a prominent part in the literature for many years, but it remained for the epochal discovery of George F. Dick and his wife, Gladys H. Dick, to demonstrate its actual rôle in scarlatinal infection. Hitherto no specific scarlatinal streptococcus had been found, and the streptococcus was generally considered to be a secondary infection. The importance of the streptococcus in scarlatinal disease was observed as early as 1884, by Loeffler, who isolated it from the throat smears of anginose cases. His observations were amply confirmed by numerous subsequent studies. Although the coccus is generally obtained from the throat in severe cases, not all severe septic cases of scarlet fever develop a streptococcic infection. When, however, it is present it is characterized by marked persistence. Smillie observed the constant presence of a true hemolytic streptococcus in severe cases of scarlet fever, but found that the organism is less likely to be present in the milder ones, and that in many instances it persisted in the throat for several months. He demonstrated the similarity of the particular strain of streptococcus ("beta" type) with that of septic sore throat, and believed that its persistence might have been the means of transmitting scarlet fever as well as sore throat. Streptococci were also found in the blood of scarlet fever patients.

Moser observed them in 63 per cent. of cases after death, but Hektoën found them in only 12 per cent. of scarlet fever patients. Although they were frequently the cause of death, there was as yet no positive evidence that they were the cause of the disease. There was little doubt at that time that the added virus of the streptococcic organism often dominated the picture and that the scarlatinal organism seemed to create a special disposition (lowered resistance) to streptococcic infection. Kolmer illustrated this by finding a low streptococcus-opsonic index during the first week of the disease. He believed that the streptococcus of scarlet fever belongs to the general class of streptococci, but that it was modified in some way during the course of the disease so as to present certain specific antibody and transitory cultural characteristics. In fact, as already remarked, streptococci were not found in all cases of scarlet fever, severe or otherwise; the severe cases being often due to the overwhelming effect of the true scarlatinal virus without secondary streptococcic infection. Moreover, the injection of strains of scarlet fever streptococci in apes did not produce scarlet fever, although the blood of scarlet fever patients transmits the disease to animals (Landsteiner). Finally, the irregular results of antistreptococcic serum in the treatment of scarlet fever sustained the doubt as to the streptococcus as the cause of the disease.

But whatever the specific microörganism of scarlet fever was destined to be, it was generally conceded that it resided principally in the upper respiratory tract, the discharges from which are the most fruitful source of contagion. The theory that the virus resides in the scarlatinal skin exfoliations has been entirely disproved by modern research. The virus is known to be particularly tenacious of life and has been supposed to be the means of infection from *fomites* many years after having been in contact with a case of scarlet fever.

The isolation of the streptococcus hemolyticus as the etiologic factor of scarlet fever marks an epoch in preventive medicine as important as any event in medical annals. For with the discovery came the susceptibility test as well as immunization and specific treatment which should provide more effective control and treatment of the disease. Although before the Dicks announced their discovery, in October, 1923, the rôle of streptococcus hemolyticus had been suspected (since it was known to be a constant organism in all scarlet fever cases), it was assumed to be a secondary factor, being concerned with the development of complications rather than with the actual origin of the disease. The idea was that the scarlet fever inciting organism, whatever it might be, made of the scarlet fever subject fertile soil for the development of streptococcic disease. Scarlet fever had as yet not been produced experimentally in the human subject and the immunity usually conferred by one attack of the disease did not appear to be characteristic of streptococcus infection.

The epochal studies of the Dicks were based on observations in the case of a nurse, who, while attending a mild but typical case of scarlet fever, developed a sore finger and two days later showed symptoms of the disease. At the height of the rash several drops of pus were obtained from the lesion on the finger. Stains were made of direct smears of the pus and detailed and careful studies were made of cultures during two weeks' incubation. The only organisms found in these cultures were

a hemolytic streptococcus and a diphtheroid bacillus. From these an apparently pure culture of the streptococcus was obtained.

The first step was fortunately followed by success in obtaining five volunteers willing to submit to inoculation with the hope of developing scarlet fever. Three of the experiments proved negative while the other two cases were reported by the Dicks as "probably caused by the hemolytic streptococcus." At the same time, however, the authors cautiously refrained from claiming that these tests justified the conclusions that all cases of scarlet fever "are caused by the hemolytic streptococcus described," although their experiments had fulfilled all the requirements of Koch's law: The organism in these cases was found specific for scarlet fever, and had not been found in any other disease; it had been obtained in pure culture from which the disease was experimentally produced in the human subject, and it had been demonstrated that the characteristic symptom of scarlet fever namely, the exanthem, is caused by the scarlatinal streptococcus. After these experiments came the discovery of the specific toxin which explained recovery and subsequent immunity as being due to the reaction of this toxin and by the formation of antitoxin, which, by neutralization of the former, produced recovery and immunity.

Thus armed the control of the disease has come within the range of possibility.

Modes of Conveyance.—The disease is communicable by *direct contact*, or through intermediaries, human beings, flies, insects and domestic animals, and by inanimate objects. There is also evidence of the milk supply as the apparent source of an outbreak of scarlet fever. But careful investigation generally succeeds in tracing the cause to the presence of the disease among the helpers or others connected with the dairy supplying the milk.

A not uncommon source of scarlet fever infection is the *carrier* of the disease who furnishes that most unwelcome type of case known as the "return case," which causes hospital authorities in particular no end of annoyance and unpleasant criticism, and which, unavoidable in a small percentage of cases, is so difficult to explain, but which bids fair to be reduced since the discovery of the specific organism of the disease and the consequent susceptibility tests and changes in treatment.

Every experienced physician has met with such return cases, the average of which is estimated at from two to four per cent. of all cases. A patient having recovered from a mild uncomplicated scarlet fever is sent home as clean, that is to say, all signs of desquamation have ceased, and there is no discharge from the nose, ears or throat. A week or two later some one in his family or in his environment develops a case of scarlet fever, apparently infected from the returned patient. When the original disease was accompanied by profuse rhinitis, otorrhœa and suppurating glands this infectivity has been known to persist for several months after the development of the disease.

There is a tendency to hold hospitalization responsible for the phenomenon on the ground that the patients are sent home too early, or that if detained too long the atmosphere of a fever hospital is conducive to secondary infection, or that owing to carelessness in bathing the patient before dismissal, or lack of precaution during transference to the home, the patient catches cold and thus, through the medium of

a catarrhal discharge from the nose, throat or ears, becomes a source of infection. If any of these were the true cause, the incidence of return cases would not be as comparatively low as it is. The question has received particularly careful attention from British physicians. It appears that not all the cases, so called, are actual return cases, that is, infection from recently discharged patients. Many of them are "incidentals" that develop at home after the incubation period from the first case has passed, either from lingering infection in fomites, or what is more likely, from unrecognized mild cases that have remained at home. This fact is often well demonstrated when a scarlet fever patient is ready to go home and, for some reason or other, is detained at the hospital. In the interim, say from two to four days, one of the members of the patient's family is brought to the hospital with the disease. If the recovered patient, instead of having been unavoidably detained, had been sent home, then this newcomer would naturally have been included in the list of return cases, whereas in reality he does not belong there. We are much inclined to agree with Arnold, who has studied the question from the standpoint of home conditions, and proves quite conclusively that the home conditions to which the majority of patients are returned have a preponderating influence on the incidence of return cases. In his very interesting study conducted at Manchester, England (1912), Arnold found that the greater number of cases of scarlet fever sent to hospitals for treatment come from homes that average more than one occupant per room and the average of susceptibles in such houses is twice as great as in homes where there is less than one person per room and where a scarlet fever patient is treated at home. This, together with the probably less intelligent and cautious after-care of a recovered scarlet fever patient (*see* p. 259) in such homes, should sufficiently explain the relatively greater incidence of "return cases" from fever hospitals as compared with "recovery cases," the term used by Arnold to describe the transmission of the disease by a recovered patient who has been treated at home. The question, therefore, to a large extent resolves itself into a social one, the solution of which is a matter of civic betterment, education and improved housing facilities. A certain proportion of these return cases being thus accounted for, it remains to explain the balance. In view of what we know of the persistence of scarlatinal infectivity, hospitalization is at fault only in so far as hospital construction and management are at fault. The ideal is, of course, to have separate rooms or small wards. Failing these, it is important to avoid overcrowding the wards. Then, also, the septic cases should be kept away from others, and should not be allowed to be sent out until all suppurations have ceased; or, in persistent cases, until a certain time limit has passed, which, of course, is arbitrary. We find a minimum of three months a good working rule for the release of patients with discharging nose and ears. There should also be separate wards for the acute cases and the convalescents, taking care, always, whether in the acute or in the convalescent stage, to keep the clean cases away from those that have discharging nose or ears. The patient should not be sent out immediately after a warm bath and, when ready to go home, should be dressed warmly and protected from draughts. The parent or guardian should receive very definite instructions as to after-care, such as prevention of cold, separation from others at home for at least two weeks, sleeping in a separate bed. With these hospital and

home precautions carefully carried out, the percentage of return cases should be limited to those that are unavoidable, owing to the persistent infectivity exhibited by some patients, which, as Caiger puts it, should be considered as part of the natural history of the disease. In spite of the susceptibility test and advances in treatment these precautions are still valid as hospital and posthospital routine.

Symptomatology.—**CLINICAL HISTORY.**—*Period of Incubation.*—The incubation period of scarlet fever is not long compared with that of other infectious diseases. It may be as short as 24 hours; it is rarely longer than a week, the average time being from 2 to 4 days. But in considering the incubation period in this as in other infectious diseases, it is well to bear in mind the distinction between contact and inoculation and the variation in susceptibility displayed by different individuals. This aspect of the question is forcibly illustrated in a hospital for infectious diseases where the attendants are constantly subject to contact, but actual inoculation—the development of the disease—may take place in a few days, or may be delayed for several weeks, months or years, or it may never take place. For practical purposes, however, that is, for lifting a quarantine in a hospital ward or an institution and allowing exposed children to return to school, it is generally considered safe to regard 8 days (after the appearance of the last case, or after exposure) as the limit of incubation.

Mode of Onset.—A distinguishing feature of the disease is its sudden onset with practically no prodromal symptoms.

Symptoms during Progress of Disease.—A child, or an adult, in apparently normal health suddenly feels languid, complains of sore throat accompanied by vomiting, headache and fever, and in 12 to 48 hours—usually in 24 hours—presents the typical red rash and a flushing of the cheeks. The lips, in striking contrast to the pallor around the mouth, often appear redder than normal. The combination of intense angina and initial vomiting is so constant a feature of the disease that even in the absence of the exanthem it immediately suggests scarlet fever. The mucous membranes of the mouth, the pharynx and the nasopharynx show a diffuse fiery-red eruption, that is, an enanthem is present as well as an exanthem. The site of greatest intensity of the enanthem is the *tonsils*, which in the severe cases appear markedly reddened and swollen and oftentimes are covered with a well-organized pseudomembrane, in many instances clinically indistinguishable from that of true diphtheria. The *nose* may show a profuse acrid discharge.

The *soft* and the *hard palate* present an uneven roughened appearance due to numerous reddened elevations or punctæ. These are of great diagnostic value in differentiating the angina of scarlet fever from other throat conditions, particularly in certain borderline cases of diphtheria. In institutions where diphtheria-scarlatina cross-infection is always a bugbear, these punctæ are especially worthy of study. They are also occasionally found in other than scarlatinal sore throat. Their absence or, rather, the presence of a pale, smooth palate is almost proof positive that the case in question is *not* one of scarlet fever.

The *tongue* presents a series of successive changes which are almost pathognomonic of scarlet fever and are of great diagnostic value. At first it is covered with a white furry coat through which the swollen red papillæ are seen to project. This so-called "white strawberry tongue" is often seen also in diphtheria and measles, but differs from the latter

in that in scarlet fever the coating begins to desquamate in a day or two and by the fourth or fifth day it is red and glistening with the papillae more or less distinctly prominent. Sometimes they are small and numerous, resembling the granulations in a wound; at other times they are scattered and more prominent. This "red strawberry or raspberry" tongue, or the fourth-day-and-after tongue, as it has been termed, persists for several days and is sometimes diagnostic as late as the seventh to the ninth day of the disease. After this the tongue gradually resumes its normal appearance. The consistency with which this desquamation takes place enables the experienced physician to tell almost at a glance and with almost invariable precision how long the disease has been present in a case seen after the initial period has passed.

The *submarillary glands* are usually more or less enlarged, hard and painful; slight enlargement of the *postcervical glands* is sometimes observed, and generally the *inguinal glands* are also involved.

The *temperature* mounts rapidly, and in about 24 hours reaches its maximum— 100° – 103° – 105° F. (37.7° – 39.4° – 40.6° C.), according to the severity of the case—at which it remains for the next two or three days, or as long as the eruption continues bright, and then falls by lysis, rarely by crisis. In the uncomplicated case this fall of temperature (by lysis) is one of the most constant features of the disease. Although a high temperature of 104° F. (40° C.) or more generally indicates a severe and possibly fatal infection, this is not necessarily so; such cases have been known to recover, while others have succumbed where the temperature curve was not unusually high.

The *pulse* is small, unduly tense and rapid, often more rapid than is warranted by the temperature; but this does not affect the prognosis. In the more severe case the pulse is small, soft and obliterated at the arterial periphery.

Respiration is affected as in all febrile diseases.

The symptoms progress during the three, four or five days following onset, after which in the simple case they begin to abate. The rash begins to fade in the same order in which it appeared, from above downward, and desquamation then sets in. But the throat condition and the swelling of the tonsils and the glands, as well as the strawberry tongue, persist into the second week.

The *rash* begins on the upper chest and spreads rapidly upward, often covering the neck, going around in front of the ears to the temples, downward to the trunk, and lastly to the extremities, increasing in intensity during the first 24–72 hours after its appearance. It is often irritating and causes the patient to scratch the skin. The region around the mouth and the center of the face, in the majority of cases, is not affected and stands out pale and triangular—circumoral pallor—in marked contrast to the rest of the face. Other parts of the body not always affected by the rash are the scalp and the palms and soles, although the latter may be deeply flushed.

Under pressure from the fingers the eruption is obliterated, the underlying skin often appearing yellow (icterus) as the finger is withdrawn. Firm pressure with the fingers of the open hand will often show white lines that quickly disappear, but reappear with greater distinctness and remain visible for a longer time. Stroking the skin with the finger-nail will show either a white line (pallor) or a red line with a well-marked

line of pallor on either side—secondary pallor. While of considerable aid in diagnosis, this secondary pallor can be accepted only as evidence, but not as proof, since a similar skin reaction often follows injections of diphtheria antitoxin or other sera.

In dark-skinned subjects, especially the negro, the eruption is often difficult to recognize. It may sometimes be seen by making strong pressure with the fingers on the soft parts (the arm or the abdomen), when it will be momentarily visible in the pallor resulting from the pressure. Oftentimes, on inspection, the palms and soles will reveal a red blush, and at the bend of the elbows, in the axillæ, the flanks and the medial aspect of the thighs a fine papular eruption will be seen.

The rash of scarlet fever varies greatly both in character and in distribution, probably more so than in any other of the eruptive fevers. It is best seen on the chest and the neck.

In the mild cases it is often evanescent and not infrequently is altogether wanting in certain parts of the body. Sometimes it begins to fade from the earlier affected parts before it has spread to the later ones, the extremities. In some severe cases also, especially where the throat symptoms are very pronounced, and in malignant cases the rash may fail to develop.

The typical eruption appears in uniform bright red (or pink in the very mild cases) punctate spots, about half the size of an ordinary pin-head, on a more or less flushed background, although occasionally the skin between the points is normal. The skin is also sometimes swollen, especially when the rash is profuse. It may appear brighter on some parts of the body (the abdomen, and medial aspects of the thighs, the elbows, the axillæ) than on others, thus giving the body a blotched appearance. This irregular eruption is often papular and macular, as in measles. It is in these cases that it is visible on the palms and soles. This variation from the usual uniform punctation is also sometimes noted on the forearms and legs, where not infrequently the rash is definitely papular, especially about the shin—a valuable diagnostic point in cases that come under observation when the rash has already begun to fade. *Miliary vesicles* with turbid contents often develop, and not rarely the rash becomes petechial, especially in the creases of the skin, the hemorrhages being closely set and minute. These petechiæ often persist for some time after the eruption has faded from other parts of the body, giving a distinctly stained appearance to the skin.

The *desquamation* is even more typical of scarlet fever than the eruption, and often serves to establish diagnosis in the mild cases where the early symptoms have been indefinite. The process of shedding extends over a period of two or three weeks or more, continuing longest over the thicker parts of the epidermis, *i.e.*, the soles and palms, always the last to clear up, and often falling off in casts from the fingers and toes. In fact, finger desquamation is pathognomonic of the disease. There is noticed at first a thickened, parchment-like feel of the balls of the fingers, accompanied or soon followed by a white line at the juncture of the pulp of the finger with the nail. The skin along this line may be separated with the examiner's finger-nail and made to peel backward, coming off very easily in large strips or casts. This sign is of the utmost value in the diagnosis of cases coming under observation in the stage of convalescence.

Like the other manifestations of scarlet fever, the desquamation also

shows considerable variation in character. It is often almost imperceptible, and affords no aid in diagnosis except in connection with the other symptoms. Often, too, it is present merely in the form of a powder which rubs off as the skin is being dried after a bath. This is especially the case in infants, but the powdery desquamation is also seen in older children at the anterior borders of the axillæ, at the lower part of the neck and between the fingers and the toes, and frequently as a little roughness on the shins.

The mechanism of the process is often described as a "pinhole" arrangement. The bursting of an inflamed skin papilla causes a breach in the skin which, at first small, increases in size and soon becomes visible as a pinhole in the cuticle; and as the process extends the increase in the size of the breaches in the epithelium and their coalescence cause flakes of greater or less size to become detached. The process is best seen on the neck and the chest and the lateral aspect of the upper extremities.

LABORATORY FINDINGS.—*Blood.*—The blood in scarlet fever shows marked leukocytosis. The increase is supposed to begin during the incubation period and to progress with the course of the disease, ranging in the mild cases from 7,000 to 34,000 and in the severe ones from 14,000 to 40,000. The differential count shows mainly an increase, both absolute and relative, in the polymorphonuclears. Eosinophils, which at first are diminished, also increase toward the third and fourth days, a phenomenon which seems to be peculiar to scarlet fever and which might serve in differentiating it from tonsillitis and other septic infections. Various attempts have been made to find a connection between a positive Wassermann and scarlet fever. But on the authority of Kolmer, who reviewed the literature on the subject and who found only two per cent. positive reactions in 250 cases of scarlet fever, no such relationship can be said to exist. Kolmer is supported by similar conclusions of other investigators.

Urine.—The urine is dark and scanty. The amount of urea excreted seems to run parallel with the fever, as much as four per cent. having been noted with a temperature of 103° F. (39.4° C.). Albumin is also present during the height of the fever. But this albuminuria is not generally considered to be related to the nephritis which is a feature of convalescence. The diazo-reaction is usually positive in the septic cases during the stage of eruption, and is sometimes regarded as a forerunner of a stormy course of the disease.

Diagnosis.—A diagnosis of scarlet fever would be justifiable when a patient gives a history of recent (within a week) exposure to infection, followed by a sudden onset of general malaise, sore throat and vomiting, the latter persisting in the severe case, but ceasing after two or three attacks in the mild case; the appearance, usually within twenty-four hours—sometimes later—of a diffuse red eruption beginning on the chest and spreading rapidly upward to the neck and downward over the entire trunk and the extremities; followed on about the eighth day—or later—by desquamation. In addition to these physical signs, the urine is dark and scant, shows slight albuminuria, and during the febrile stage, excess of urea excretion. The blood shows marked leukocytosis with marked eosinophilia during the early days of the disease.

A diagnostic adjunct of considerable value is represented by the Schultz-Charlton blanching reaction or extinction phenomenon published

by these observers in 1918. They found that an intracutaneous injection of 1 c.c. of normal blood serum into a scarlet fever patient with a bright rash produces characteristic skin changes. In about six hours after the injection there appears a complete blanching of the rash over an area from one to several centimeters in diameter. The outline of the blanched area is irregularly oval and its color that of the normal skin and may remain quite visible for several days. This phenomenon has been more or less generally adopted by the profession. The reaction is assumed to be due, according to its originators, to a normal property of human serum which is temporarily lost during the acute stage of scarlet fever and is regained during convalescence. Therefore the following rule can be formulated: If a serum gives a positive Schultz-Charlton reaction it is not from a scarlet fever patient (presumably in the first two weeks of the disease); if the serum fails to give the reaction it is from a scarlet fever patient. The reaction, in fact, has a double diagnostic value; for Schultz and Charlton observed also that serum from fresh scarlet fever cases does not give the reaction.

Mulson believes that the Schultz-Charlton reaction represents a toxin-antitoxin phenomenon, with certain points of resemblance to that of diphtheria.

Like most tests which are dependent upon human serum, the Schultz-Charlton reaction, when first introduced, presented certain difficulties, especially to the general practitioner, which made it more or less unsatisfactory. Fortunately this objection has been overcome since the introduction of scarlet fever antitoxin which various biological houses and drug concerns are now furnishing for diagnostic as well as for prophylactic and therapeutic uses. The diagnostic, or Schultz-Charlton, dose of 0.1 c.c. of the antitoxin is injected intradermally, the technique being the same as for the Dick test (see p. 256).

Although the extinction phenomenon test offers a rather reliable diagnostic method, especially in doubtful cases, and even though the typical case is rather easy of recognition, nevertheless the physician may encounter atypical pictures, where the symptom-complex is not clear. Oftentimes only a few of the aforementioned features may be present; at other times the picture is suggestive of disorders that are also associated with throat symptoms and the appearance of a rash, so that every practitioner at some time or other finds himself confronted with the question of differential diagnosis.

DIFFERENTIAL DIAGNOSIS.—In its very *early stage* scarlet fever may suggest a simple *tonsillitis*, *quinsy* or *influenza*, and occasionally *acute lobar pneumonia* may be mistaken for scarlet fever. But simple tonsillitis is rarely associated with initial vomiting, and the general disturbance is not apt to be very pronounced, while in quinsy the swelling in the throat is distinctly local, and usually unilateral. There is rarely an eruption associated either with tonsillitis or with quinsy beyond a very slight, non-punctate erythema on the arms, chest and back in tonsillitis, and an urticarial septic, blotchy, also non-punctate rash on the elbows and knees in quinsy. But often the eruption of *scarlatina anginosa* is also blotchy and the punctations are indefinite. In such cases differentiation is not easy, and would rest on the absence of desquamation, a slower pulse and the presence of severe frontal headache. The absence of marked throat symptoms should help to distinguish influenza from scarlet fever. Usu-

ally rapid respirations in connection with suspicions of scarlatina before the eruption has appeared should lead to an examination of the lungs before a positive diagnosis is made; but often the physical signs of a lobar pneumonia do not appear for several days. The appearance of the rash, however, should clinch the diagnosis.

In the *eruptive stage* the differentiation must be made from other acute exanthemata—measles, rubella, varicella, and the eruptions due to drugs, sera, sepsis, gastro-intestinal and other toxemias.

The confusion of *measles* with scarlatina often rests on a scarlatinal rash in the former and a multiform eruption, especially in the septic type, of the latter. On the other hand, occasionally in severe cases of scarlet fever there is a combination of morbilliform and scarlatinal rash (double eruption); should there be a concurrent coryza or conjunctivitis the difficulty of diagnosis would be enhanced. Again, in measles, at the beginning of defervescence the rash sometimes assumes the diffuse punctate character of a typical scarlatinal eruption. Differential diagnosis in such cases thus is a matter of circumspection and caution, especially where both types of eruption are simultaneously present.

Generally speaking, the differentiation can be made on the following basis: the incubation period of 10 or 12 days in measles compared to the 2 or 6 days of scarlet fever; the more diffuse and less punctate character of the rash which is preceded a day or two by the appearance of typical Koplik spots in the mouth; swelling of the face; the predilection of the rash for the face; absence of circumoral pallor. These, together with the spread of the rash behind the ears, distinguish measles from scarlet fever. The skin, after the acute stage is passed, shows a characteristic "coppery" or "mottling" pigmentation. As for desquamation, it is only the shedding of large scales that can be taken as positive evidence of scarlet fever.

The rash of *rubella* comes out in discrete spots, but often on about the third day, owing to coalescence of the individual maculae, the eruption may resemble a real scarlatinal erythema from which it is scarcely distinguishable, indeed often absolutely indistinguishable. The throat symptoms, generally mild or absent, may be severe, even show a tonsillar exudate, and in some cases the fever may run high. But usually the fever is low and the pulse much less rapid compared to the temperature than in scarlet fever. Differentiation rests on the long incubation period (two or three weeks), the more evanescent character of the rash, the absence of tongue symptoms, as well as of circumoral pallor. Desquamation is unusual in rubella. The glandular enlargement differs from that of scarlet fever in being slight and usually painless: the glands are hard and discrete and sometimes cause a stiffness of the neck: involvement concerns the cervical, postcervical and in many cases the axillary and inguinal glands.

Varicella frequently presents a prodromal rash strongly resembling a scarlatinal eruption. The differentiation can usually be made on the mild onset, slight, if any, throat symptoms, the condition of the tongue and the absence of desquamation. However, the true varicella vesicles appear early, indeed generally are the first signs of the disorder, and there is frequently the question to be considered of the simultaneous presence of the two diseases.

Variola also shows a prodromal scarlatinal rash, but this is rarely punctate and is more irregular and faint. Throat and tongue symptoms are not pronounced: backache is most marked and constant, and should help in differentiation.

The irregularly distributed *erysipelatous* rash is hardly likely to be mistaken for the lobster rash frequently seen in scarlet fever, especially as in the former the face is uniformly puffy and congested in appearance.

Drug rashes are often caused by coal tar products, the salicylates, quinin, opiates and resinous substances, such as copaiba. The rash, however, is usually blotchy and well defined against the skin, compared to the gradually fading off of a scarlet fever rash. The most frequent cause of drug rash is the use of belladonna, whether given by mouth or in the form of a plaster or instilled into the eye for ophthalmic and other purposes. The eruption is erythematous, rarely punctate, and is followed by desquamation which may be powdery or may resemble the typical pinhole desquamation of scarlet fever. There is generally a transitory fever and delirium together with dryness and redness of the throat and more or less dilatation of the pupil; but the absence of tonsillar enlargement and of scarlatinal punctæ on the palate and of tongue symptoms, together with the history of the use of the drug, should serve to differentiate a drug rash from scarlatina.

The rashes due to *sepsis* and to foods causing gastro-intestinal and other *toxemias* may occasionally be scarlatiniform, but the absence of temperature and of throat symptoms, as well as the history of ingestion of certain foods—shell fish, strawberries, tomatoes, etc.—and of a personal idiosyncrasy, should remove any doubt as to the true nature of the eruption. Desquamation is also distinctive, usually beginning before the rash has entirely faded; it may be repeated several times at the same point and may include the hair, the finger-nails and the toe-nails. The skin after desquamation is brawny and red in contrast to the soft pink skin seen after scarlet fever desquamation.

Serum rashes of a scarlatiniform type are not unusual, and when occurring in the diphtheria ward of a hospital are a source of endless trouble; so much so that prompt and complete isolation of diphtheria patients presenting such a rash is imperative. The differentiation of serum rashes from the eruption of scarlet fever is discussed at page 158.

In the *desquamating stage*, differentiation must be made from other disorders such as rubella, serum rash, simple erythema, which are associated with more or less profuse shedding of the skin. The most reliable item is the history of the case which, if it includes one or more of the usual complications of scarlatina, should decide in favor of the latter.

Complications and Sequelæ.—The complications of scarlet fever are troublesome, often stubborn, and not infrequently are the direct cause of death. Many of them are referable to aggravation or extension of the existing pathology which forms part of the symptom-complex of the disease, such as rhinitis, otitis, glossitis, scarlatinal rheumatism, etc. A strict classification into symptoms and complications is, therefore, not always practicable. Other complications appear late, during or after convalescence. These, then, may often with justice be considered sequelæ of the fever.

Of the early complications one of the most common, and probably the most intractable, is *rhinorrhœa*. Destructive processes of the posterior nasal mucous membrane are manifested by a mucopurulent or a serous nasal discharge which is irritating and highly infectious and the persistence of which often delays convalescence and prolongs quarantine.

The infectious period, especially in young children, is also often unduly prolonged by *aural complications* which are said to take place in

from 10 to 15 per cent. of scarlatina cases. The trouble may or may not be initiated with pain and fever and may vary from a trivial inflammation of the external canal, with possible involvement of the membrana tympani, and transitory deafness, to the more frequent manifestation of a typical otitis media, followed by a more or less profuse and persistent mucopurulent discharge. About 75 per cent. of severe cases of scarlet fever with pronounced throat and nose symptoms are said to be complicated by serious ear troubles. In the writer's experience, following conservative local treatment, this percentage has been markedly reduced.

The *aural complications* of scarlet fever may arise at any time from the fourth day to the third week, or later. *Otitis media* usually sets in during the third week but may also appear later. While infection may be carried by the blood stream, it is undoubtedly most often transmitted through the eustachian tube, and too often is the result of the pernicious practice of forcible syringing of the nasal passages.

The prognosis of otitis media is favorable, although in a percentage of cases, especially among young children, the suppurative process leads to *mastoid disease* often with superficial abscess formation. Mastoiditis is manifested by tenderness, swelling and redness behind the ear, and protrusion forward of the auricle which often stands out almost at a right angle to the head; also by fever and its accompanying symptoms. Sometimes there is a peculiar edema of the eyelid and over the zygoma on the affected side. Generally there is early evidence of pus formation beneath the periosteum; and at times exfoliation of bone. The condition yields rapidly to surgery.

Among unusual conditions due to an extension of otitis media may be mentioned *meningitis*, *cerebral abscess*, *thrombosis of the lateral sinus*, *pyemia* and *deafness*, the latter the result of irreparable injury to the middle-ear structures.

In rare instances collections of pus in the tonsils or sloughing of the throat in the anginose cases may lead to *retropharyngeal abscess*. This requires prompt drainage in order to avoid serious results—suffocation, septic pneumonia, generalized pyemia—from the pressure of the pus, or ulceration and possible rupture of a vessel from burrowing of the abscess.

Hemorrhage in scarlet fever, though rare, should be included among its complications. While exceptionally it may be due to a hemorrhagic diathesis, it is more likely to result from extension of the necrotic process to one of the larger vessels. The hemorrhage may be arterial, venous or capillary, its frequency being in the order mentioned; it may also be arteriovenous. Erosion of one of the larger vessels is the most frequent cause of bleeding. The erosion may be large or small, with rough edges, and may vary in size from one millimeter in diameter to a sieve-like perforation. Hemorrhage from internal organs (liver, heart, spleen, stomach, lungs) may also take place, as well as from subcutaneous tissues with a more or less hemorrhagic pleural and pericardiac exudate. The outcome of this complication is usually death. Fatal otitic hemorrhage is very rare in scarlet fever. It has, however, been known to appear with out any warning signs whatever, such as mastoiditis, facial paralysis or the like.

Synovitis scarlatinosa, or scarlatinal rheumatism, is a frequent complication of scarlet fever, occurring in about three per cent. of all cases,

their appearance during the third or fourth week, the critical time being the 19th to the 22d day. The most interesting of these later complications are lymphadenitis and nephritis.

Lymphadenitis, a glandular enlargement usually independent of faucial or other lesions, often follows a primarily mild case of scarlet fever. Its onset is sudden, marked by rise in temperature together with more or less pronounced glandular and periglandular swelling and tenderness; the trouble is generally unilateral, and affects the cervical and the submaxillary glands; sometimes both at the same time. The inguinal and axillary glands may also be affected. The acute symptoms usually subside in two or three days, but a subacute affection may persist for several weeks.

This lymphadenitis often is an important aid in diagnosis in limited epidemics in institutions and hospitals where only a few cases of scarlet fever develop, and some inmates have apparently escaped infection. The subsequent appearance of lymphadenitis among the latter would establish a diagnosis of previous scarlet fever, although the primary symptoms have been unobtrusive. These slight and aberrant cases are as capable as the severe and typical ones of undergoing the changes in the general condition which are responsible for the development of the complications and sequelæ of scarlet fever.

The prognosis of lymphadenitis is favorable. Even when accompanied by suppuration, recovery is prompt following free incision and drainage. Prognosis, however, is not so good when, as often happens, the adenitis is associated with nephritis.

Scarlatinal nephritis is justly regarded as the bugbear of scarlet fever. Its incidence depends on the severity of a given epidemic. On the average, it is supposed to complicate from 10 to 15 per cent. of all cases. Like lymphadenitis it seems to prefer the milder cases and is often the first sign of the previous existence of scarlet fever. This scarlatinal nephritis, as a rule, presents the clinical picture of acute hemorrhagic nephritis. Its onset is sudden, accompanied by a rise in temperature, vomiting, headache, loss of appetite, a feeling of fullness in the abdomen, but rarely abdominal pain. The face presents a peculiar pallor. Edematous swelling of the eyelids is sometimes the first symptom of nephritis. There is tenderness in the kidney region and occasionally a slight enlargement of the kidneys is palpable. The urine is scant in amount, dark, and in severe or advanced cases may be distinctly hemorrhagic in color. It contains albumin, blood, free red blood corpuscles and hyalin and granular casts. The specific gravity is increased and chlorids are diminished. The symptoms generally reach their climax in two or three days and subside gradually; they usually disappear at the end of two to four weeks, leaving perhaps a more or less persistent anemia. The renal disturbance in these favorable cases seems to have little effect on the heart, except for slight bradycardia, or a slow, tense pulse after defervescence, and increased blood-pressure.

Sometimes the symptoms of nephritis, albuminuria, for example, persist for many weeks, although the patient seems to be making favorable but slow progress toward recovery. This persistence indicates continued rest in bed, for it is only reasonable to assume that the pathological changes produced by the disease are healing slowly or perhaps incompletely, although the functional derangement may have been sufficiently overcome as to present no great disturbance.

The great danger of nephritis, of course, is *uremia*, which often supervenes without any prodromal signs until convulsions set in. Sometimes, however, there may be headache, nausea, or vomiting, loose stools, nocturnal unrest, slow pulse with increased tension, to indicate impending uremia. Some patients also show a peculiar staring expression or slight mental confusion just before the convulsive attacks appear. The temperature also rises after the appearance of the uremic symptoms, and represents the climax of the nephritis and dominates prognosis. In dragging cases of nephritis, if the patient is able to overcome the uremia, recovery finally takes place. But often death ensues either as the direct result of the toxic condition, or from complications caused by the same—pneumonia, pleuritis, cardiac weakness and a consequent pulmonary edema. The latter, in fact, is a more frequent cause of death than the uremic convulsions.

In spite of the aforementioned serious possibilities, the prognosis of postscarlatinal nephritis is, on the whole, favorable. Complete recovery, though it may be retarded for a year or more, is the rule in practically all cases, a fact confirmed by the most recent studies of this question.

Before leaving this subject of complications and sequelæ of scarlet fever it should be stated that literature contains numerous observations of pathological conditions accompanying or following scarlet fever which are claimed to be the direct result of the disease. We believe, however, that such observations are merely coincidences. Among such accidental associations may be mentioned appendicitis, peritonitis, diabetes mellitus, suprarenal lesions, sinusitis, hyperthyroidism, neuralgias and many others.

RELAPSES, RECURRENCES AND SECOND ATTACKS OF SCARLET FEVER.—The distinction of these terms is often an arbitrary one, but it is usual to consider a relapse or recurrence as referring to cases in which a recrudescence of the disease appears either before convalescence has set in, or during convalescence, while a secondary attack denotes cases in which the patient experiences a true scarlet fever at a more or less remote period after recovery from the first attack.

Relapses or recurrences are unusual. Collected statistics show an incidence of 0.1 to 0.5 per cent. of all cases, the greater number occurring in fever hospital wards where the constant addition of fresh cases keeps the air more or less surcharged with infection. A relapse or recurrence should be regarded as such only upon positive evidence of a primary attack. No indefinite symptoms should be accepted as indicating a true antecedent scarlet fever. Recurrences usually appear during the third or fourth week, generally around the 25th day. The symptoms are those of the original attack—vomiting, angina, fever, rash, desquamation—and may present the same peculiarities and variations. It is a general impression that the severity of the recurrence is in inverse ratio to that of the primary affection, that is, a light attack is likely to be followed by a severe one and vice versa. The prognosis, however, of the secondary illness is usually good, although death during such an attack has been reported.

The question is often raised whether these secondary attacks are instances of reinfection or of imperfect elimination of the primary infection. They are in all probability the latter, that is to say, incomplete immunization: for a patient cannot be considered as cured until immunization is complete and the disposition to scarlet fever is definitely

overcome. Sometimes this immunity is delayed and the patient goes through more than one relapse. Welch has observed two recurrences in the same patient, eighteen and fifteen days respectively elapsing between the several attacks. Caiger reports a case which suffered three relapses within three months, the last one proving fatal.

Although one attack of scarlet fever is supposed to render the subject immune for life, this immunity may be lost later on and a *second attack* may take place at any time. Such second attacks have been observed by the writer at periods varying from six weeks to fifteen years after the first one.

Association with Other Diseases.—The association or coexistence of two or more infectious diseases is not unusual. Scarlet fever may be associated with diphtheria, measles, varicella, whooping-cough, mumps, erysipelas, variola, typhoid, in the order of frequency as enumerated.

Sometimes on the second or third day of the scarlatinal disease a rapidly spreading exudate develops on the tonsils and from there spreads to the entire throat, to the nose, the mouth, the eustachian tube, and may even involve the middle ear. This *membranous angina* was formerly known as scarlatinal diphtheria, but cultural studies have shown that it is not due to the diphtheria bacillus, but is of streptococcic origin.

The presence of the Klebs-Loeffler bacillus in cultures of such exudates would, of course, establish a diagnosis of *diphtheria* in conjunction with scarlet fever. The combination occurs much less frequently in private cases than in hospitals; but in modern institutions where culturing the throat effluvia of all scarlet fever patients is a routine measure, and where facilities are at hand for isolating and observing patients, the phenomenon has been considerably reduced in recent times. Postscarlatinal diphtheria is discussed on pages 140 and 148 of this volume.

The simultaneous appearance of the exanthemata of *measles* and scarlet fever is one of the puzzles of fever hospital management. A diagnosis of double infection based on the appearance of the rash alone should be made with caution. As has already been indicated, the rash in scarlet fever is often morbilliform, while in measles it may assume a punctate character on certain parts of the body. Sometimes the two rashes are simultaneously present. Diagnosis in such instances depends upon the development of symptoms pathognomonic of each of the two diseases—lacrimation, coryza, Koplik's spots for measles; scarlatinal angina, tongue symptoms and desquamation for scarlatina. There is no rule as to the priority of the two diseases. It is generally claimed, however, that prognosis is good when measles develops after scarlet fever, but not so good when scarlet fever follows measles.

The association of scarlet fever and *varicella* is not uncommon; in fact, it is said to be the most frequent combination of two acute exanthemata. When simultaneously present the probability is that varicella is the primary disease. Diagnosis, as a rule, presents no difficulty in view of the difference in character of the two eruptions; often it can be established on an enanthematous throat lesion—the typical varicella palate, or the scarlatinal angina.

Scarlet fever developing after a varicella eruption is well established is probably a case of mixed infection, a possible avenue for the second infection being a ruptured varicella or other skin lesion. The author has seen one such instance, and several have been reported by other ob-

servers. Scarlet fever following varicella is supposed to run a more benign course than does a varicella following scarlet fever.

As to the other infectious diseases mentioned, the symptoms may develop at any time during the course of the primary disease, but are supposed to set in more often when one or the other infection is beginning to subside.

The combination of simultaneous or concomitant infections is not limited to two; triple infections are not uncommon and quadruple ones not unknown. In fact, their number may be as many as the infections to which a given individual has been exposed, though they do not necessarily all appear during the acute stage of one or the other disease. We have seen scarlet fever combined with varicella and whooping-cough; with diphtheria and measles; with diphtheria, measles and epidemic cerebro-spinal meningitis; also scarlet fever, diphtheria, varicella and whooping-cough; and scarlet fever, diphtheria, varicella and measles; with recovery.

Clinical Varieties.—While suddenness of onset distinguishes all cases of scarlet fever, the severity of the initial symptoms varies and usually corresponds to the severity to be expected in the subsequent course of the disease, which may be mild, moderately severe, or severe, the types being generally known as scarlatina simplex, scarlatina anginosa and scarlatina maligna. Other varieties are surgical scarlatina, puerperal scarlatina; some authorities also recognize a scarlatina sine exanthem as a clinical type of the fever.

SCARLATINA SIMPLEX.—In the *mild type*—scarlatina simplex—the symptoms, including the eruption, are often so vague as to cause little, if any, disturbance until the onset of complications or the beginning of the desquamation stage, which often too is slight, appearing as a fine white powder over the neck, the shoulders and the chest, at the tips of the fingers and between the fingers and the toes. Sometimes the typical rash is merely transient, unaccompanied by fever, while the throat is only moderately injected and swollen and gives scarcely any discomfort. Such cases may be missed altogether and remain undiagnosed until some one who has been in contact with the patient develops the disease in a more pronounced form or the patient himself experiences a subsequent attack of nephritis or other complications. For it should be remembered that these cases, in themselves so mild, are subject to the same complications—otitis, nephritis, etc.—and may be just as infectious as the severe types. They thus represent a serious menace and a fruitful source for the spread of the disease.

In the febrile cases of this mild type where the rash is less evanescent, the temperature, at first sub-normal, rises to about 100° F. (37.7° C.), as the rash develops, and then on the second or third day falls to the normal and remains there.

In the *moderately severe* type all the symptoms are aggravated. The temperature rises quickly to 103° F. (39.4° C.), or more, the pulse is very rapid, the rash appears promptly, remains more or less intense for four or five days, when it begins to fade and usually disappears by the sixth or seventh day, by which time the fever also usually has subsided. The throat is redder than in the milder case, the tonsils, the uvula and fauces are involved, as are also the lymph glands at the angle of the jaw and the mouth, and swallowing becomes difficult. Small yellow patches often appear on the tonsils, but are not distinctly membranous

and are easily wiped off. It is in these cases that serious ear trouble is apt to supervene. There may also be a seropurulent discharge from the nose, irritation from which excoriates the anterior nares and the upper lip. The inguinal glands are almost always involved, to some extent. During the height of the fever there is much thirst, restlessness and occasionally delirium. Though the patient is much prostrated and often anemic, barring complications, recovery usually takes place.

The *severe* forms of scarlet fever, as a rule, are ushered in with severe symptoms, and are usually divided into a septic type—scarlatina anginosa, and a toxic type—scarlatina maligna.

SCARLATINA ANGINOSA.—The throat condition is impressive and determines the seriousness of the case. The throat is patchy. Small flakes of exudate appear first on the tonsils, and as the disease progresses cover the tonsils and spread to the surrounding parts upward as far as the soft and the hard palate and downward into the larynx, in some rare instances causing a degree of obstruction requiring intubation.

The mucosa of the mouth is intensely congested and sometimes is the seat of ulcerations. Sordes develop on the teeth and lips, the latter becoming dry and cracked; ulcers of the aphthous variety show on the tongue, and fissures develop in the corners of the mouth.

The eruption is nearly always well developed. A frank eruption is most desirable, indicating good heart action; in fact, prognosis is unfavorable when the punctæ of an intense eruption are irregular in size and in distribution.

The severe symptoms persist from seven to fourteen days even though the eruption has begun to fade or has faded. The purulent discharge from the nose is profuse and irritating and is often transferred by the nails of the patient to other parts of the face, causing a local pustulous eczema. When the skin about the eyes becomes thus infected the result is a marked cellulitis, the swelling both in degree and color often suggesting erysipelas.

The enlargement of the cervical and submaxillary glands is marked, causing great discomfort, so that the patient makes no attempt to clear the throat and when compelled to swallow grasps his neck in trying to ease the pain caused by the act. There is also a typical tendency to throw the head back to relieve the pressure caused by the swelling.

This type of patient is very ill, and if a child, is exceedingly irritable and restless, and very difficult to manage and to keep in bed. Delirium is marked, in fact, often wild enough to require restraint; dullness and apathy, as in typhoid fever, are exceptional. Anorexia is complete. This is the type of scarlatina that is frequently complicated by suppurating glands or discharging ears.

In some cases of this type of the disease the predominant symptoms are those of a general septic condition; oftentimes, too, they present a combination of throat symptoms with general sepsis. In rare instances the pharyngeal inflammation is gangrenous followed by sloughing which may expose or even open the large vessels, with fatal results.

Variations in temperature are often due to the development of one or the other of the complications that nearly always accompany the disease and frequently cause death after the patient has successfully thrown off the primary infection.

SCARLATINA MALIGNA.—Stormy onset and rapid development of se-

vere toxic symptoms ending in death in a few (usually 12-24) hours characterize this fulminating, but fortunately rare, type of scarlet fever. Intense headache and cerebral symptoms, often with convulsions, usher in the attack, but the most prominent symptoms are diarrhea and persistent vomiting. The temperature rises rapidly, often going as high as 106° F. (41.1° C.), and even 108° or 110° F. (42.2° or 43.3° C.), and remaining high until the end or just before, when it may fall to sub-normal. The pulse-rate not uncommonly is 160-170, with a soft, weak, irregular pulse, and feeble heart sounds. The urine is scant and albuminous.

The disease runs its fatal course so quickly that usually the rash hardly has time to develop; when it does make its appearance it is indistinct, scattered and dusky. The throat symptoms also are sometimes limited to a mere redness of the fauces, and there is often absence of glandular involvement. The patient is stuporous, with low muttering delirium; the cheeks are hollow; the eyes lusterless and oftentimes covered with a thin film. Just before death there is frequently a general lividity of the skin, especially on the trunk, which may take on a dark purple hue. Few patients survive beyond three days.

SURGICAL SCARLATINA—PUERPERAL SCARLATINA.—These are generally mentioned as clinical varieties of the disease, although there is much discussion as to the validity of the classification. Some authorities are inclined to regard them as cases of scarlet fever occurring in the wounded or in the parturient woman. Others feel justified in grouping them as cases presenting an atypical portal of entry of infection, through an open wound or through the genital organs, instead of through the pharynx.

SCARLATINA SINE EXANTHEM.—Scarlatina sine exanthem, if accepted as a clinical entity, well illustrates the fact that of all the infectious diseases there is perhaps none that shows so many deviations from the typical as does scarlet fever. The exanthem, as we have already stated, may fail to develop. The diagnosis in such cases is often made *ex post factum*, i.e., on the appearance of desquamation, the development of complications—adenitis, nephritis, with or without a history of an antecedent sore throat—or by the occurrence of a case of true scarlet fever in the family or in the environment of the patient. The fact that these cases show immunity when subsequently exposed to contagion is also offered as an argument in favor of including this among the clinical varieties of scarlet fever.

Treatment.—In the management of a communicable disease the physician finds himself in a most unique position, in that not a single but a three-fold duty confronts him, i.e., a duty to the patient, to the community in general, and to himself. The first concerns his professional skill in the matter of treatment; the other two concern the no less important question of prophylaxis. Hitherto isolation was practically the only means of controlling scarlet fever. But efficient isolation is particularly difficult in this disease, being as it is one of the most insidious of the acute infections, and one that cannot always be diagnosed unless seen at the crucial time, so that many cases are overlooked. Not only that, but what makes it more dangerous is that the light cases which are often unrecognized may be more fruitful as sources of the spread of the disease than the severe ones. Thus any subject of scarlet fever may become a public health menace. Furthermore, difficulty of control is much enhanced by carriers who cause "return cases," and who, as is well known, may be instrumental in starting an epidemic.

The spread of infection is more easily controlled in those diseases for which the causative agent is known. Until scarlet fever found a place among such infections the demand for precautionary measures was much more insistent than at present. But for the sake of communities where modern methods of prophylaxis and susceptibility tests are not yet in vogue we offer the rather rigid suggestions for prophylaxis that have hitherto been demanded.

PROPHYLAXIS.—Isolation of the patient, of course, is imperative. Children and others who have been exposed to infection should be kept away from school and from other children or from contact with other individuals until the incubation period is safely passed. There is no objection to allowing the well children of the family to remain at home if the isolation and quarantine requirements are adequate and *are respected*. The father of the family or other breadwinners may be permitted to attend to business, provided it does not entail contact with children or young people, and provided, of course, that any proximity to the sick-room is conscientiously avoided.

At one time the prophylactic use of **streptococcic bacterin** seemed a rational measure, before the identity of the causative agent was known. The method found favor in Russia where it was introduced by Gabritschewsky in 1905. At the Philadelphia Hospital for Contagious Diseases it was tested in order to immunize diphtheria patients against outbreaks of scarlet fever in the diphtheria wards, and was found to be of little value.

According to the experience of Di Cristina, the desquamating scales of scarlet fever patients apparently contain an antibody which, if injected subcutaneously, seems to ensure immunity to scarlet fever. He was led to make the test, following the demonstration by Caronia (1914), of a specific antigen in the extract of desquamating scales of a scarlet fever patient and guinea-pig complement which induced the deviation of complement reaction. The test seemed to be positive in all stages of the disease, and served in differential diagnosis. Di Cristina thereupon prepared a vaccine of convalescent serum 15 c.c., desquamated shreds and scales 10 grams, to which were added phenol 0.8 per cent. and 1 c.c. guinea-pig complement, the whole being incubated for fifteen minutes at 37° C. (98.6° F.), centrifuged, put into vials and sealed. Ten children who had never had scarlet fever were given subcutaneous injections of 1 c.c. of the vaccine every second day; the deviation of complement reaction occurred after a second or third injection. The children were casually exposed to the disease and none developed it. A similar immunity was exhibited by some children who by mistake had been put into a scarlet fever ward of the hospital, inoculated twenty-four hours later, and allowed to remain in the ward. Di Cristina and Pastore in 1919 report forty successful instances of this prophylactic use of the vaccine. Children were allowed in the room with scarlet fever patients, even sleeping in the same beds with perfect immunity. The cases were followed up for six months, and the continued presence of the immunity was confirmed.

We give the above as a matter of history. We have had no experience with the method nor do we know of any tests that confirm Di Cristina's statement. Moreover all such methods have been superseded by the present means of prophylaxis and treatment, *i.e.*, the Dick test for susceptibility, the use of the toxin for active, and of the antitoxin for pas-

sive immunization. These means, although so recently placed within our ken, have rapidly gained foothold in active public health work.

The Dick test for susceptibility is carried out in a manner similar to that used for the Schick test for diphtheria (see p. 154), and like it is dependent upon the ability of the subject to neutralize a small amount of toxin obtained from the strain of streptococcus which is known to cause scarlet fever.

Once having established a susceptibility test, the next logical step is immunization of susceptibles. While it is too early to say how long active immunization will last, it is thought by some to be effective for at least one year and may, in all probability, last a lifetime, especially as it is a well-known fact that susceptibility to the disease decreases naturally after the twentieth year of life. Active immunization is now sufficiently developed to warrant rather definite conclusions with regard to its permanence and the author advocates its use as a routine measure. Park, in a valuable contribution to the subject, remarks that he believes that those who pass the Dick test are probably immune for many years, and most likely for life. The dosage is not altogether standardized. Some authorities recommend four doses at intervals of one week, the first one consisting of 600 skin test doses, the second of 2,400, the third of 6,000, and the fourth of 12,000 skin test doses. Or it can be given in three doses, 500, 5,000 and 30,000 skin test doses, respectively, at ten-day intervals. Children under two years of age should receive one-half the usual dose. A skin test should be made two weeks after the last dose to determine whether active immunity has been obtained. The injections are made subcutaneously, with a sterile syringe and a fine needle, into the arm at the insertion of the deltoid muscle.

Immediate and temporary, or passive, immunity provided by the use of scarlet fever antitoxin rests upon quite firm ground. At the Philadelphia Hospital for Contagious Diseases passive temporary immunity has been carried out with satisfactory results in more than a hundred Dick positive cases after varying degrees of exposure. Preparations from five different biological manufacturers were used and the serum was given in one injection on an average in 48 hours after exposure. The dosage used was as follows: In children under four years of age antitoxin to neutralize 50,000 skin test doses of toxin was given; from the fourth to the sixth year inclusive, 75,000 skin test doses; and to all over six years, 100,000 skin test doses. All the cases gave a negative Dick test when re-tested 72 hours after the administration of antitoxin, and not one of the series developed scarlet fever during an average of from four to sixteen days' subsequent stay in the hospital. There were no control Dick tests made for duration of immunity. In about the same number of additional cases exposed to scarlet fever (through having been sent in under the erroneous diagnosis of scarlet fever) but with negative scarlet fever histories, antitoxin to neutralize 100,000 or more skin test doses was given. The cases all had had direct and most intimate exposure to scarlet fever in the ambulance, or in the wards with active scarlet fever cases, varying in time from five to sixteen days, and not one of them developed scarlet fever.

In the light of present day experience it is safe to endorse the use of scarlet fever toxin for producing active permanent immunity. It is particularly called for in institutions where children are housed as well as for nurses in training schools and whose work may expose them,

sooner or later, to scarlatinal infection. The use of the antitoxin is recommended as an agent for passive immunity, as an emergency prophylactic in families and more particularly in hospitals and other institutions where scarlet fever may already have developed, and threatens to become an epidemic.

When scarlet fever develops in a school or institution the patient should be **isolated at once**. With careful observation of the other inmates and their examination at least twice daily by the public health authorities, and prompt isolation of all suspicious cases or close contacts, such as room-mates, it should not be necessary to close the school or institution, unless the disease threatens to assume epidemic proportions. To avoid this the facilities for such isolation should be of the very best, otherwise it is better to remove the patient to a fever hospital or to a private home, as the case may be. This question of providing for isolation and observation in schools and child-caring, as well as other institutions where young people are housed, is one of the most vital problems of public health administration. It is our conviction that no such organization should be granted a charter unless adequate arrangements for the complete and safe isolation of suspected cases are included in the plans of their building or buildings.

As to the precautions to be taken to prevent the spread of scarlet fever which develops in the ward of a general hospital or in a ward other than the scarlet fever ward of a hospital for contagious diseases, a full consideration of this question would not fall short of a complete discussion of hospital management and construction. In a general way it may be said that safety demands, of course, instant isolation of the patient. Next in importance is the separation from each other of all contacts until each one has safely passed the incubation period dating from the time the last case of the disease has been removed. This separation, to be effective in limiting the number of secondary cases that may arise, should be as complete as arrangements permit, use being made of every available room or side-room connected with the exposed ward. Or, in the absence of accommodations other than the ward itself, quarantine may be successfully managed, when the room is large, by keeping the children in different parts of the room, separated by screens. They should under no circumstances be allowed to mingle with each other. Their meals should be served to each separately. When using the toilet and bath they should go in one at a time. These patients should, in fact, be considered as occupying separate rooms, and no one in attendance should go from one patient to another without changing cap and gown and washing the hands well with soap and water. These may seem like super-refined precautions, but fortunately the incubation period of scarlet fever is short, and the extra trouble entailed is not great. It is worth while, if for no other reason, for the satisfaction of knowing that each patient has been accorded the fullest possible protection.

In modern fever hospitals with ample observation facilities such as obtain, for example, in the Philadelphia Hospital for Contagious Diseases, this plan of separating contacts can be carried out in an almost ideal manner, a separate room being provided for each person. Where this is not feasible the next best thing to do is to classify the contacts, placing the less susceptible with the more susceptible. For instance, it would be better to place a child with an adult than to put two children

or two adults in the same room; or a young child under five—the more susceptible age—had better be placed with an older child over ten—the less susceptible age—than with a child its own age or younger; similarly it is better to have an acute patient with a convalescent than to have two acute patients together.

Sometimes in a general hospital the question arises of sending contacts home. At first such a proposition may seem hardly worthy of attention. But on consideration it has much in its favor, if the cases that are to be sent home are judiciously selected. By doing so we not only protect the exposed child or children whose vitality is already lowered by some disease or other, but at the same time we are reducing the chances of secondary cases arising by just so many as are sent home. In other words, not every contact in such a ward is infected at the first round, but he may get the infection from the second or third or any subsequent case that may develop. Sending him home removes that chance in a certain percentage of instances. On the other hand, if the contact has been incubating the disease and develops it in his own home, he would have developed it just the same in the ward of the hospital, where the chance of infecting already weakened children is much more of a menace. But, we repeat, the cases to be thus sent home must be very carefully selected with full regard to the type of case, the home surroundings and other details.

Measures less drastic than the foregoing have sometimes proved sufficient, such as merely disinfecting the bed of the patient who has been removed, and the adjoining beds or, as is sometimes done in European hospitals, treating the patient behind a closed screen, on the theory that infection is not air-borne. We mention these measures only to condemn them, since first of all, there is no positive evidence that infection is not carried in the air, and secondly, even if such evidence existed it is always better to err on the safe side, and surely so in scarlet fever, for which, of all contagious diseases, no half-way prophylactic measures are ever justifiable.

If the patient is to be treated in his own home, isolation should be as complete as circumstances permit. A most essential point and one that should be insisted upon whenever at all practicable is that the sickroom be provided with separate toilet facilities. The sickroom should be removed as far as possible from the rest of the house; the choice would be an entire floor at the top of the house. Where this is not feasible an ideal arrangement is that described by Griffith, consisting of the sickroom and an adjoining room which opens into a third room or hall, the windows in all three rooms being well screened, in order to prevent possible spread by flies and insects. Keeping the windows in the anteroom open as much as possible provides what amounts to an out-of-door passage between the sickroom and the rest of the house and prevents possible aerial convection. All the doors of the sickroom, except the one leading to this adjoining room, should be tightly closed and the cracks and key-holes stuffed with cotton or pasted over with strips of gummed paper, such as is used by disinfectors. The door of the anteroom communicating with the rest of the house should be kept closed when not in use for the purpose of exit or entrance. Hanging a sheet soaked in disinfectants (5 per cent. carbolic or 1/1000 sublimate solution) at this door is not of much, if any, protective value, but may

be useful if for nothing else than to act as an ocular reminder that a quarantine is on and should be respected.

The furnishings of the anteroom should be limited to the most necessary articles, but they should by all means include a clothes-tree, washstand, bowl, soap, towels, etc.

The sickroom should be stripped of all unnecessary furniture, hangings, clothing, etc. Only such toys or books should be allowed to remain as are of negligible value and can be burned.

The attendant or nurse should wear a dress and cap of washable material. When leaving the patient she should change her clothing in the outer room, wash her hands well with soap and water, gargle her throat with **liquor antisepticus**, or some other mild disinfectant, and if she is going out, she should leave the house without coming in contact with any of the family.

In this anteroom, also, the doctor, before entering the room, should remove his coat, put on a washable cap and a gown, which completely covers him. Wearing a mask is a wise precaution as a protection to himself and as a prevention against his becoming a possible carrier of the disease through the agency of his mucous membranes. After having seen the patient he should remove his protective outer garments in the anteroom, wipe off his shoes, disinfect and wash his hands well with soap and water, taking care to get the soap well under the fingernails. All instruments which he has used, he will, of course, carefully sterilize. It is best to use wooden tongue depressors and applicators which, being inexpensive, can be burned. The doctor should endeavor to make this his last visit for the day, and in any case should again wash his hands before approaching the next patient.

The nurse should have her meals served in the anteroom rather than take them with the family. Her tray can be placed outside the sheeted door. Before taking it in she should wash her hands and put on a cap and gown. After she has finished her meal she can again set the dishes outside the sheeted door whence they can be removed and can with safety be washed in the kitchen. For her own protection she will not eat in the sickroom unless her constant presence there is imperative on account of the desperate condition of the patient—delirium, etc. In that case she should be provided with special utensils and dishes which she places outside the sheeted door and to which her food is transferred by a member of the household, great care being taken during the process of transference that her special dishes are not touched. After she has finished her meal she sterilizes and washes her dishes ready for the next meal. These same precautions also apply to the handling of the patient's food at all times.

The patient's bedclothes and his personal wear should be soaked for at least an hour in a disinfecting (carbolic or sublimate) solution, and after being wrung out of this can be thrown out of the window to be gathered up, or can be placed outside the anteroom door. They then can be safely washed with the household linen, if necessary.

Nothing should be allowed to be taken from the sickroom that has not been thoroughly disinfected. This applies particularly to excreta and any effluvia from the patient. For the nasal and other discharges, instead of handkerchiefs, pieces of gauze should be used, and these, as well as all soiled dressings, should be burned. In short, nothing from the infected zone should be placed in a clean zone, unless previously disinfected.

Instead of the carbolic solution which is expensive, Griffith suggests the following stock solution: carbolic acid (Calvert's No. 4), 6 fl. oz. (180 c.c.) and glycerin 4 fl. oz. (120 c.c.); adding 2.5 fl. oz. (75 c.c.) of this to water to make one quart (one liter) gives an approximate 5 per cent. solution.

After the patient has recovered and is ready to leave the room he should be given a cleansing bath, consisting of a generous soap and water lathering of his head and entire body; after this he is wrapped in a sterile sheet and taken into the anteroom, where he gets another soap and water bath. The throat and mouth should be cleansed with a bland mouth wash, such as Dobell's solution, as a gargle and retained in the mouth for several minutes; and after being dressed in clean clothes, the patient should be allowed to vacate the sick room.

In view of the uncertainty regarding the duration of the infectious period of scarlet fever, it is well not to allow the patient to sleep with any one for, at least, two months. It is best that kissing be dispensed with. If insisted upon it should be done on the forehead, but under no circumstances should the patient be kissed or kiss others on the mouth. He should be kept from other children for at least two weeks or as much longer as is convenient, and should spend as much time as possible in the open air. Especial care should be taken to guard a recently recovered scarlatina patient from exposure to draughts, chill, wet feet or any condition that may cause him to catch cold. The resulting discharge from the nose is apt to bring down germs that may be lurking in the many convenient hiding places in the nasopharynx.

This after-care of the patient is essential in every instance on account of its bearing on the vital question of preventing return cases (*see* p. 238).

It is here that the social worker, who should form part of the staff of every modern hospital, including fever hospitals, and the visiting nurse prove of inestimable value. A word of advice and an objective demonstration of the measures needed to safeguard the child and its associates are nearly always more effective than written instructions. The social service department established at the Philadelphia Hospital for Contagious Disease, has given ample demonstration of its worth.

After the patient has left the sickroom the latter should next receive attention. In our opinion all that is necessary is thorough cleansing with soap and water of the walls, furniture and other articles, although renovating the walls and refinishing the furniture add to the sense of security. The mattresses and pillows can be effectually sterilized by exposing them to the sun for several days. Subjecting them to a steaming process is of questionable value, but can be done if desirable.

Solely on the principle that the infectious agent of scarlet fever resides in the discharges from the nose, throat, ears and suppurating glands, and that in their transference lies the danger of disease-spread, prophylaxis naturally resolves itself into measures that prevent such transference, the mechanical means for which are direct contact, intermediaries—doctor and nurse, inanimate objects, air (in a limited sense), insects, domestic animals. As to the prophylactic technic to be observed we have here limited ourselves to the most essential features, but they are of the utmost importance in the performance of the aforementioned threefold duty of the physician. If rigorously carried out the danger of infection is reduced to a minimum; indeed, it is practically *nil*.

GENERAL MANAGEMENT.—The general management of the scarlet fever patient consists of **rest in bed** as nearly absolute as possible. Even in the mildest sort of case the patient should be kept in bed for at least four weeks in order to avoid exposure to draughts and sudden changes of temperature, thus reducing the risk of complications, such as nephritis, rhinitis, etc. In fact, it is better to keep the patient in bed during the entire course of the illness. The exception to this would be young children, not under the constant control of a nurse, who when not under supervision might get out of bed and suffer exposure. In such instances it is better to have the child dressed warmly and allow it to be up. Another exception would be on warm days when the patient, child or adult, could be wheeled out to a sunny porch.

The temperature of the sickroom is a matter of opinion. We find that the mildly acute cases seem to do well at a room temperature of 68° to 70° F. (20° to 21.1° C.). But for the very severe case, especially the septic one with hyperpyrexia and delirium, a lower temperature is desirable—55° to 60° F. (12.8° to 15.5° C.), or even less when the air is dry, crisp and clear. The patient's bed should be kept as close to the window as possible and protected from draught by a screen (behind the bed) or sheets draped around the bed or crib, and the window kept open except in damp, stormy or blustery weather. The patient should wear flannel bedclothes and have his head wrapped in heavy flannel or a blanket, leaving only the face exposed. Sometimes, as a protection against cold air circulating under the bed, an extra mattress as well as hot water bottles at the feet of the patient will be needed. The bed coverings should be warm but not heavy, fewer being required during the height of the fever than later on. With every precaution for keeping the patient warm the room temperature can, with advantage, be kept at less than 55° or 60° F. In fact, **fresh-air treatment** has everything in its favor. Where feasible this may even be interpreted to mean open-air treatment.

A daily sponge bath with tepid water and soap is essential. It adds not only to the comfort of the patient but assists in elimination and in restoring the skin to a normal, healthy condition.

Inunctions are of no curative value, but are useful in relieving the itching and preventing the scattering of the exfoliating skin.

Careful attention to obtaining a **daily bowel movement** and **ample urination** is of the utmost importance. For the former, **castor oil** may be given to children of four years or less; **magnesium sulphate** to older children or adults; or **pulvis glycyrrhizæ compositus** which is more pleasant to the taste. In addition to this the severe septic case with hyperpyrexia and delirium should have a **daily colonic irrigation**, preferably in the evening just before the patient is being prepared for the night. In the milder case and for all cases during convalescence an **enema** once a week is of advantage.

For the *kidney elimination* **free fluid intake** is essential. An average of one and one-half liters should be given (more or less according to age); adults, if they so desire, may have **carbonated waters**. If the fluid cannot be taken by mouth it should be given per rectum or in desperate cases by means of **intravenous injections of salt solution**. The daily output should be measured and a routine examination, microscopic and chemic, should be made at least twice a week or oftener if convenient or desirable. The information afforded by frequent urinary

examination gives the doctor confidence as to the course of the disease and enables him to change or to increase the diet accordingly, especially where the patient rebels against the restricted régime in scarlet fever.

During the acute stage in severe cases it is well to bear in mind the possibility of *acidosis* as a contributing toxemia. For this reason **tests for acetone and diacetic acid** should be made when the patient's appearance—sunken listless eyes, sighing respiration, air hunger and restlessness—suggests the presence of acidosis. **Alkalis** are the indicated treatment, and it generally meets with prompt and satisfactory response.

Sleep is most essential, and on no account should the patient be disturbed for treatment, feeding or any other purpose.

The **diet** should receive careful attention at all times. During the vomiting stage of the disease it will do no harm to withhold all food. After that a milk diet is an ideal one and should be adhered to, whenever possible. The average case can be kept on milk, as much as the patient will take, every three hours, and orange or other fresh fruit juices once a day until the temperature has been normal for seven to ten consecutive days. After this, if the kidneys are functioning well, both as to quantity and quality of output, the diet may gradually be increased to include cooked cereals, the pulp of stewed fruit, toast, bread and butter and light puddings. Very soon vegetables may be added, such as spinach, baked white potato, celery. Weak tea and coffee are permissible to those accustomed to their use. No further increase in the diet is advisable until after four weeks or until all danger from nephritis is passed. Sometimes, however, the severer cases with protracted fever, emaciation and weakness will require the low diet to be earlier supplemented by strengthening food; oftentimes this is followed by marked improvement.

In cases of persistent vomiting, **rectal feeding** may have to be resorted to, and sometimes when the throat symptoms make swallowing difficult, **nasal feeding** will have to be tried. But this drastic measure is rarely necessary, for with tact and patience on the part of the nurse the difficulty may be momentarily overcome.

Little, if any, *medication* is required for the ordinary case of scarlet fever. The majority do well on rest in bed, sleep, fresh air, a daily sponge bath, careful feeding, plenty of water, laxatives as needed and a bland mouth wash. Various drugs have been recommended, such as **biniodid of mercury, salicin, salvarsan**, but their efficacy has not been proven. The only medication we use as a routine measure during the febrile stage of scarlet fever is **citrate of potassium** given in large amounts of water every three hours, in full doses to adults, and 1 grain (0.065 gram) for every year of the child's age. After the temperature has been normal for four or five days **Basham's mixture** may be substituted for the potassium citrate. During convalescence, when the patient is on a more liberal diet, **syrup of iodid of iron, combined with syrup of hypophosphites**, is useful as a tonic; for marked wasting, **emulsion of codliver oil and malt** is beneficial.

Outside of the foregoing, medical treatment is purely symptomatic. We have already called attention to the desirability of a frank expression of the *rash*, since it indicates good heart action. In order to bring this about in cases where the rash is scant and ill-defined, the use of **hot-water bottles, hot packs, or wrapping the patient in heated blankets** is recommended. This can be done even though the temperature runs

high, since the elimination that results helps to reduce the temperature and also diminishes the patient's restlessness.

For the *fever*, as long as the case appears to be a simple one and the temperature does not go above 102° F. (38.9° C.), an **ice cap** to the head (except for infants) is all-sufficient. It also suffices where the temperature is 103° or 104° F. (39.5° or 40° C.), but is not accompanied by stupor, jactitation or other nervous symptoms. In the presence of the latter **hydrotherapy** is indicated. For this purpose we do not advocate cold, but prefer **warm water**, the choice being the **warm pack** repeatedly given. There is no objection to sponging with tepid water, but it is not always agreeable, especially to the young child, and is not so easily given nor so soothing as the warm pack. This is given in the usual way, by wrapping the patient first in a sheet wrung out of warm water and then in a blanket.

But often, in the toxic and the anginose case especially, hydrotherapy fails to relieve the delirium and the patient remains restless and loses sleep. In this event every effort must be made to induce sleep the importance of which cannot be overemphasized. **Bromids** in full doses will suffice in some cases, but for the more stubborn ones the best hypnotics are **whiskey and chloral**. **Trional and veronal together with whiskey** have also proven useful. But these drugs should not be given by any one but the physician in attendance. Oftentimes a **dose of whiskey** will diminish the restlessness and induce drowsiness, if not sleep. This may be given in hot sugar water in doses suitable to the age of the patient: 1-2 fl. dr. (4-8 c.c.) for a child between two and four years; double the amount for one between four and eight years; and three times the quantity for children from eight to twelve years of age. Beyond this age 1 fl. oz. (25-30 c.c.) may be given up to fifteen years; while adults may have 1-2 fl. oz. (30 to 60 c.c.). We cannot agree with those who believe that whiskey is harmful in that it favors the development of nephritis, for we find that just as many, or more, mild cases that are not given whiskey develop nephritis as severe ones that have received it.

If after two or three doses the alcohol fails to produce the desired effect it may be necessary to resort to **chloral**. We repeat, its administration should not be entrusted to any one in attendance, no matter how experienced, except the physician. He alone must assume the responsibility for the certain amount of risk entailed by the use of the drug. The risk, however, must be taken, since sleep must be obtained and promptly obtained in order to save the patient's life. It is remarkable how well these delirious, restless toxic cases tolerate chloral. In fact, by some authorities it is supposed to act as a direct antidote to the scarlatinal poison. The dosage is regulated according to the age of the patient, varying from 2 grains (0.13 gram) of the hydrate in a little water for a child between two and four years up to 30 grains (2 grams) for an adult. It should be repeated every hour or two until drowsiness is produced, but great care should be taken not to push it to the point of poisoning. A sudden fall in temperature and weakening of the pulse indicate that the point of tolerance has been reached. The drug should at once be withdrawn and **hot coffee, per rectum**, be given to avoid collapse. Sometimes the combination of **bromid and chloral** is effective and obviates the necessity for a larger and possibly dangerous dose of chloral. When especially indicated, stimulants, such as **strychnin**,

whiskey, caffen, camphor, may be given, but they will be required only in severer cases.

The *throat symptoms* will next demand attention. Mild symptoms in a young child had best be left untreated. For an older child, able to gargle, it is well to use a solution of **normal saline or liquor antisepticus alkalinus**, N.F. Local treatment by irrigation, syringing or swabbing is strongly condemned except in certain conditions. For example, when the patient is an adult or a child old enough to coöperate, irrigation with normal saline as hot as can be borne may be allowed; or when ulceration takes place, it is permissible to use gentle applications of one-fourth strength **saturated solution of potassium chlorate or tincture of iodine**, twice daily, to the affected parts only. This, however, should be done only by an experienced person who is impressed with the necessity of extreme gentleness in the use of this measure. Better than this and much to be preferred is the use of a **spray** since it means less trauma from manipulation and less danger of introducing infection. A very valuable solution for this purpose consists of the following:

Rx Aq. hydrogenii peroxidi (Aq. hydrogenii dioxidi)	f ʒ v (150.0 c.c.)
Ipecacuanhe vini	f ʒ iii (12.0 c.c.)
Glycerini	f ʒ v (20.0 c.c.)
Aquæ	q.s. ad f ʒ viii (240.0 c.c.)

For the *prevention of general sepsis* too much attention cannot be paid to the routine measure of keeping the mouth and nose, the portals of entry of infection, in an aseptic condition. Asepsis in this connection rests on cleanliness and the avoidance of irritation. The value of antiseptics is very questionable; if used they should be highly diluted, in order to prevent irritation to the delicate and already devitalized mucous membranes. Any skin lesions, such as burns or wounds, should also receive strict aseptic treatment, since they likewise present favorable avenues for the entrance and spread of infection.

The *mouth, gums and teeth* should be cleansed gently twice daily with a **cleansing, non-irritating solution**, such as Dobell's; or if preferred, a solution of either salt, or borax, or bicarbonate of soda, alone or combined with 10-20 per cent. glycerin, may be used. In case of *mucous membrane infection* which is apt to occur in mouth-breathers, the cleansing of the mouth should be followed by some **oily solution**, such as liquid albolene, to allay or prevent irritation to the delicate mucosa. The condition of the *teeth* is of vital importance. Whatever can be done during the course of the scarlatina to remedy defects, such as collections of tartar, carious teeth, etc., should be done, for the teeth as a persistent source of infection is to-day a matter of common knowledge. All **necessary dental work should be attended to** before the patient is discharged from the hospital.

The *asepsis of the nose* is just as important as that of the mouth but often presents some difficulty, especially when infection extends to the nasal vault and the nasal sinuses. Forceful syringing is absolutely contra-indicated, as it is apt to spread infection. **Gentle mechanical cleansing** with a swab is permissible. If the patient is able to blow the nose he should be encouraged to do so; **ointments and medicated oils** are recommended for their protective and mild antiseptic value. In certain cases where the nasal discharge is profuse and the patient is stuporous

or otherwise unable to coöperate, we have kept the nose open by means of a **syringe and catheter**.

Enlarged tonsils and adenoids also often act as sources of persistent infection. Their **removal** as early as possible in the acute stage is advocated by some authorities and is said to have proven beneficial.

The **routine inspection and treatment of the nose, mouth and throat** are essential also, because they permit early recognition and prompt attention to *complications* that may occur, such as rhinorrhea, tonsillitis, diphtheria, measles (Koplik's spots) and other rare conditions, such as abscess, peritonsillar or retropharyngeal. For, in spite of the most careful management, complications in scarlet fever can often not be avoided. These should be treated as they arise.

For the *cracking of the lips* which though not serious, is troublesome, **compresses of camphor water** or of the preparation of **hydrogen peroxid, glycerin, wine of ipecac and water**, mentioned on page 264, are, in our experience, more efficacious than ointments. It may sometimes be necessary to put the **child's arms in splints** in order to prevent picking and consequent infection of the lips.

For the *aphthous stomatitis* which often appears on and under the tongue in cases in which, for some unaccountable reason, the temperature remains around 100° to 101° F. (37.8° to 38.3° C.) the **same solution** may be used as recommended for the throat. **Spraying the extruded tongue** is the most convenient way of treating such sores.

Rhinorrhea, one of the most intractable complications of scarlet fever, is best treated conservatively. Encouraging the patient to blow the nose is better than irrigation. Instillations of 15 per cent. **argyrol**, we have tried with indifferent success. **Insufflations of calomel** are also recommended by some physicians. In order to *facilitate drainage* we have found it advantageous to use the following solution:

R	Menthol	grains ii	(0.13 gram)
	Iodi	grain i	(.065 gram)
	Camphoræ	grams iii	(0.20 gram)
	Eucalyptol	f 3 ss	(2.0 c.c.)
	Liq. albolene	q.s. ad f 3 i	(30.0 c.c.)

M. et S.: Five drops to be instilled into each nostril three times daily.

It is when rhinorrhea persists past the fifth week, in otherwise uncomplicated cases, and renders the patient a most probable carrier, that the **excision of adenoids or enlarged tonsils** is called for, and will in most instances result in a cure.

For the *eye complications*—conjunctivitis, blepharitis, ulcerative keratitis, the latter the only one that may prove serious—the treatment is the same as when these arise in other conditions.

In the rare instances in which membranous or ulcerative laryngitis occurs intubation or tracheotomy may have to be resorted to. The differentiation of these cases from diphtheria is discussed on pp. 140, 251.

Serious ear complications can often be avoided by conservative treatment of throat and nose troubles (*see* p. 264). We mention only to condemn such practices as **nasal irrigation, palpation of the nasal vault for adenoids, forcible washing of the throat, faulty (Trendelenburg) position**, etc. *Acute swelling and obstruction in the nose* can be prevented by **instillations** of the solution mentioned above. Sometimes **inhalations of 1 8000 adrenalin** may be of service. But in spite of all precautions otitis media may arise, very often owing to the presence of adenoids or

large turbinates which act as contributing factors. The treatment of the nose and nasopharynx has been indicated above. In addition to this, any *perceptible bulging of the drum membrane* demands **immediate free incision** which may and should be repeated as often as required to maintain free drainage. As long as the drainage is sufficiently free nothing more will be necessary, for this generally relieves the condition with no further treatment except external cleansing and keeping the canal free. Any additional local treatment, should it be found desirable, should be applied only by the doctor in attendance or by a specialist, and never without the aid of the head-mirror and the speculum.

We do not advise **irrigation** except where the discharge is thick and interferes with free drainage. In such an event **irrigations of warm boric acid or saline solution** 100°–105° F. (37.8°–40.6° C.) may be used as often as required in a given case. For a thin discharge Place suggests the following **dry treatment** instead of irrigation: the ear is frequently sponged with sterile cotton and a narrow wick kept to the drum, but not so as to fill the canal closely, and supplemented, if desired, by insufflations or instillations of 5 per cent. boric acid in 15 per cent. alcohol solution.

It is only by the **early treatment of ear symptoms** that the more serious complication of mastoiditis can possibly be forestalled. Should it develop, the prompt application of **external heat** (hot-water bag) and vigorous attention to obtaining **free drainage** may sometimes avoid operation. The use of **ice-bags** is advocated by some practitioners. This, however, is indicated only at the very inception of mastoiditis, and as the exact time of that stage is most uncertain, we feel it is safer to dispense altogether with the use of cold applications.

A marked redness, swelling or tenderness behind the ear together with indications of systemic disturbance, high temperature, etc., that persist for more than 48 to 72 hours, demands operation—**excision of the mastoid cells**—at this stage. Any more radical surgery that may be required, owing to a chronic condition developing, should be deferred until after the purely scarlatinal symptoms have disappeared, and then should be done by a competent surgeon.

Much of the general management of scarlet fever is directed toward *avoiding postscarlatinal nephritis*. In this connection it may be observed that in a large series of cases we studied the blood-pressure, in the hope that it would afford some warning of an incipient nephritis, but the results did not fulfill our expectations. In spite of all precautions nephritis will develop in about 10 per cent. of the cases, although the incidence varies with the severity of a given epidemic. When it occurs it should be combated by energetic and vigorous measures. The patient, if he has been out of bed, should be immediately **put back and kept in bed** for at least three weeks. **The diet should again be rigidly limited** to milk and free intake of water. Later on, when the ravages of the disease have caused emaciation and anemia, although the urine may not yet be altogether free from albumin, the diet should be increased by the addition of foods of low protein content, that is, chiefly carbohydrates and fats (to be served with little or no salt), such as green vegetables (except asparagus), bread and unsalted butter, stewed fruits, cereals, light puddings. Sugar should be freely given. There seems little doubt but that the withdrawal of salt from the diet acts favorably in reducing any dropsical swelling. It is natural therefore to assume that a salt-free diet should also aid in preventing the development of edema.

The bowels should be kept freely open. For this purpose we generally use for adults and older children, **magnesium sulphate or pulvis jalapæ compositus**, and for children of four years or less, **oleum ricini**.

As long as *diuresis* is satisfactory **free intake of fluids**—water, lemonade and mineral waters of low salt content—is **advisable**. A palatable substitute for lemonade and one that is cheap and easily made is the Imperial Drink used in England. It consists of potassium bitartrate, 2 drams (8 grams), sugar, 1 oz. (31 grams), the juice of one lemon, added to one quart (1 liter) of boiling water, thoroughly mixed. This, diluted to taste, can be placed at the bedside of the patient for him to take at will, not alone for any specific action of the drink itself, but with the idea of encouraging the free intake of fluid.

With the appearance of *oliguria* (500 c.c. urine in 24 hours) the **fluid intake should be somewhat restricted**. For *diuretic purposes* we recommend the routine administration of **potassium citrate and ammonium acetate solution**. Later on these may be substituted by **Basham's mixture**.

Diaphoresis, especially when the amount of urine is reduced, is of the utmost value because it produces free elimination and thus helps to lift the burden from the crippled kidneys. It can be employed in the form of a **hot wet pack, vapor baths or electric light baths** and, according to the exigencies of the case, at intervals of every four hours to once daily, repeated until the urine has been found negative on four consecutive days. After this it may be gradually discontinued and the **diet** correspondingly increased.

The **hot pack** can be given as follows: Protect the bed with a rubber sheet or a cotton quilt folded. Two folded sheets are then wrung out of hot water, several degrees hotter than desired for the application, one of the sheets is laid on the bed and the patient is placed on it, the other one being used to cover him, care being taken that it comes in contact with all the skin surfaces, especially in the kidney region. The arms should be wrapped in towels wrung out of hot water, and the pack covered with heated blankets or a quilt. From twenty to forty minutes is the average time for keeping the patient in a hot pack.

The **vapor bath** can be given by heating water over an alcohol lamp under the bed, and conducting the steam through rubber tubing placed between the covers of the bed.

In our opinion the most practical form for giving these sweats is the electric bath. It is less depressing, less liable to produce burns, and more easily arranged with less exposure of the patient. A practical apparatus is one devised by Tracey, consisting of a frame or cradle covered with asbestos and provided on the inside with six or eight electric light bulbs connected by a long cord which can be attached to any electric light socket. The frame fits over the patient's body, and when in use is covered at both ends to keep the heat in. The heat can be regulated by turning on the lights and reducing the number used in case it becomes too great.

To-day when even the smallest village is lighted by electricity this method of sweating is often much easier to procure than a large amount of hot water and all the paraphernalia for giving a hot pack or a vapor bath. The apparatus is simple and portable and can easily be included in the **armamentarium** of the physician.

With the proper vigilance and conscientious study of the case on the part of the physician, neither edema nor uremia should develop in a case of scarlatinal nephritis. In some rare instances, however, in spite of all precautions—including frequent and careful urinalysis—these undesirable phenomena may supervene. In such an event *edema* can generally be controlled by **reducing the liquid intake, withdrawing salt entirely from the food, providing for free watery catharsis, and administering diuretics, potassium citrate or ammonium acetate solution.** If both of these are used in the same case they should be given alternately every two hours. Active counterirritation with **dry cupping** followed by **poultices of mustard and flaxseed** in the proportion of 16 to 1 will be useful. The poultice should be applied as hot as possible and should be large enough to cover the entire kidney region.

Symptoms of uremia or of impending uremia, such as mental apathy, drowsiness or coma, headache, delirium, muscular twitchings, disturbance of vision, marked reduction in urinary output, convulsions, require **energetic and quick action.** If convulsions set in, prompt measures are demanded for their control and to prevent their recurrence. The patient should immediately be placed in a **hot pack or a warm bath, 104° F. (40° C.).** Offering **chloroform for inhalation** in small whiffs helps to relax the patient. **Venesection** is important for reducing the blood-pressure and should be resorted to as promptly as possible. It may or may not be followed by **intravenous injections of salt solution**, opinions being divided as to the necessity for the latter. We find that most patients do well without it. The **blood** can be taken from the arm of the patient either by **incision or by aspiration**, about 100–200 c.c. being withdrawn from a child up to ten years, or 300 c.c. for an older child or an adult. This generally gives temporary relief and also gives time for other measures, such as **diaphoresis and purgation**, to act. Vomiting can be controlled by allowing the patient to swallow **small pieces of ice.** **Colonic irrigation** with a quart (one liter) of hot water assists in eliminating toxins and prepares the bowel for rectal medication, such as chloral or chloral and bromide. If there is any doubt as to the *free action* of the *bowels*., a **hydragogue cathartic** should be given, such as magnesium sulphate or elaterium for adults, and in desperate cases also for children. This can be administered through the nose by means of a catheter if the patient is unconscious. We have tried **lumbar puncture followed by injection of a solution of magnesium sulphate in sterile water**, as is done in tetanus, but the results have not proven of any great value.

When the patient revives, it is essential that he be kept very warm, by the measures already indicated. The treatment then is that of acute nephritis. *As improvement sets in*—as evidenced by increased urinary output and reduction of albuminuria—the **heat of the bed can be gradually reduced and the diet cautiously increased.**

The *cervical adenitis* that accompanies a mild case of scarlet fever requires no treatment, since it usually subsides with the acute symptoms. For the more pronounced cases various remedies have been recommended, such as **ichthyol, methylsalicylate, iodine petrogen, colloidal silver**, but their efficacy is doubtful. **Cold applications** may be helpful, but as in mastoiditis, only in the very early stage. If used, great care should be taken that the ice-bag fits snugly around the affected parts and does not

rest on the chest, as so often happens. We at all times prefer **heat**, either by the water-bag or the electric pad, or fomentations. In our experience heat does not favor suppuration; in the milder cases it promotes resolution, while in those that would break down under any treatment the process is hastened. When the process is complete—but not until then—an incision in the fold of the neck should be made. The incision should be fairly free in order to insure prompt healing with a minimum degree of scar. When the destruction of the gland has once begun it must go on to completion, and **too early incision** would prolong the process and also afford opportunity for secondary infection.

The *cervical cellulitis* that develops in the severe anginose cases is best treated with **hot fomentations**. Early incision will not prevent sloughing of the skin and the subcutaneous cellular tissues; it is best therefore to wait until the skin has softened, or according to some authorities, until it has broken down. The underlying slough should be removed with great care, and any particles that may not have separated from the healthy tissues should be allowed to come away of themselves, since force of any kind is apt to induce troublesome hemorrhage. After incision, the **wound should be treated on the usual surgical principles**. Only the blandest solutions, such as saline or boracic acid, should be employed. **Irritating solutions and packing** tend to aggravate the process of sloughing and reduce the chance of recovery which in these cases, at best, is unfavorable.

The development of so-called “*collar-neck*” or “*bull-neck*” demands **free incision** along the sternomastoid muscle, since very often a small amount of pus collects deep in the neck behind the sternal attachment. It is therefore important to **explore and drain that region**.

SERUM THERAPY.—Of equal importance with immunization is the effective treatment of the disease, and it is only natural that this should have been worked out along the same lines as the treatment for diphtheria, that is, by an antitoxic serum.

Without dwelling upon the merits of the two main sera at present in use—the Dick serum and the Dochez serum—we are free to state that serum treatment of the disease has proven efficacious in a large enough series of cases to establish its value. By its use we are able to obtain a more rapid subsidence of toxæmia, more rapid fading of the rash, more prompt return to normal of the mucous membranes, a reduction in the incidence of carriers, and a softening of the menace of return cases. The author has given the serum intramuscularly in doses the equivalent of 250,000 to 1,000,000 skin test doses, the size of the dose being regulated by the age of the patient, the degree of toxæmia and the severity of the throat symptoms, the last of which is a practical basis for estimating the severity of a given case of scarlet fever. In the use of the concentrated antitoxin now available the question of serum sickness is not a serious one. The reactions are more severe than those obtained from diphtheria antitoxin; however, no immediate serum reaction has occurred and serious symptoms have been rare.

Formerly serum therapy of scarlet fever was indicated only in the severely septic and toxic cases which, yielding to no other treatment, generally progressed with such fearful rapidity to a fatal ending. But with the means already at our disposal and with further development in technique of manufacture and better standardization of the serum and dosage, we are in a position to predict effective control of scarlet fever;

indeed, this control should undoubtedly prove even more effective than that of diphtheria. This belief rests on definite facts. Early diagnosis and consequent early treatment are essential for the best results in both diseases. So true is this of diphtheria that the observation was made long ago that antitoxin, given in proper dosage and within twenty-four hours after onset, will bring about a cure in every case.

In diphtheria the subjective symptoms at the onset are usually mild until the condition is already dangerously advanced, and the objective symptoms are concealed in the throat,—so that the disease oftentimes is not recognized until too late for antitoxin treatment. In scarlet fever, on the other hand, the onset is stormy and incisive and the main objective symptom, the rash, is a flaming signal which in from 75 to 80 per cent. of the cases appears within twenty-four hours of the onset of symptoms and sometimes shows with the very first symptom of the disease. This leads to earlier diagnosis and to more prompt antitoxin treatment than is possible in diphtheria and thus gives a start of at least one day as compared with diphtheria. If we could get this same advantage in handling diphtheria cases, the mortality could be reduced by about one-third of the present rate.

As to the present status of scarlet fever control, we have a susceptibility test which in our experience is quite reliable; a treatment for active immunization which is pretty well established and quite generally endorsed by the profession; a treatment for passive immunization of definite power as an emergency measure, and finally the supreme measure of specific serum treatment. The last named, as has been shown, not only saves life but definitely lessens the duration of the disease as well as the incidence and severity of complications. This means an enormous saving of time, money and anxiety to the patient and to his family, and eventually to the community at large. From a public health point of view the use of the antitoxin should necessarily reduce the number of scarlet fever carriers and consequently lessen the incidence of the disease itself. Serum treatment thus is both therapeutic and prophylactic, so that the day is almost at hand when scarlet fever will have lost its menacing character and as a result there will come modification of public health measures and quarantine laws with regard to this hitherto much dreaded infection.

Thus we have overcome the obvious restriction to a general application of serum treatment due to the fact that the experimental production of scarlet fever has been satisfactorily demonstrated. Before this time, however, in view of the prominent rôle of the streptococcus in scarlatinal infection, it was but natural to seek the use of antistreptococcic serum in the endeavor to combat the disease. The earliest attempts in this direction by Marmorek, in 1896, proved of no value, and while later (1903) Moser and his followers reported satisfactory results with the use of a polyvalent serum, this and similar methods failed on account of the large doses required and the difficulty of obtaining a reliable serum.

Following these experiments human blood and blood-serum derived from convalescent or recently recovered scarlet fever patients, as well as normal human blood, were used with satisfactory results, notably by Reis and Jungmann, and Koch, abroad, and in this country by Zingher, Weaver and others.

Zingher's method consisted in obtaining fresh human blood (convalescent or normal) from a parent or near relative, by means of a 30 c.c.

record syringe and a (preferably 17-18 gauge platinum-iridium) needle inserted in the median cephalic vein at the bend of the elbow of the donor. The required amount is rapidly aspirated and immediately citrated by adding the blood to a 10 per cent. sodium citrate solution in the proportion of 30 c.c. of blood to each c.c. of the citrate solution, making a 0.33 per cent. final dilution of the citrate. When the syringe is full, it is detached from the needle which is not removed, but is kept in place by an assistant who attaches to it a 5 c.c. record syringe containing a 1 per cent. sodium citrate solution to keep the needle free from blood. In this way three or four syringefuls of blood can be obtained before it becomes necessary to wash out the larger syringe with sodium citrate. The blood is collected in 100 c.c. bottles, each of which contains 2 c.c. of sodium citrate solution. To each bottle 60 c.c. of blood are added. This is then shaken to distribute the sodium citrate. The required amount, 120-130 c.c., can be thus obtained in less than ten minutes.

The recipient is given intramuscular injections of the blood (at one sitting) into the triceps, the lateral region of both thighs (*vastus externus*), the calves (*soleus*) and both gluteal regions; the dosage being 15 c.c. for a young child and 30 c.c. for an older child or an adult, at each of the three sites of injection.

The use of human blood-serum derived from convalescent patients gave excellent results, according to a report by Kling and Widfelt, during a severe and protracted epidemic of scarlet fever in Copenhagen, which lasted from August, 1916, to May, 1917. The serum, which these authors claim is both antitoxic and bactericidal, was drawn from patients four to seven weeks after the onset of the disease, 200-300 c.c. of blood being drawn off by means of a coarse aspirating needle inserted in a vein at the bend of the elbow. The serum was separated from the clot after forty-eight hours, after having been subjected to Wassermann and other bacterial tests and rendered antiseptic with 0.05 per cent. carbolic acid. It was then placed on ice for two or three weeks (it was found useful even after two months). One injection proved sufficient in nearly all of the 237 severe cases in which it was used. When possible, the injection was made into the vein of the recipient, otherwise intramuscular administrations were used, 20-25 c.c. for children under five years of age; 40-60 c.c. for older children and adults. In uncomplicated cases the effect was seen within twenty-four hours by a marked fall in temperature and in the pulse rate and marked general improvement. In the complicated ones the action was less pronounced, but nevertheless, satisfactory improvement in the general condition was noted. The treatment with convalescent serum did not appear to affect the incidence of postscarlatinal nephritis, but other complications, such as otitis, mastoiditis and lymphadenitis, seemed to be more common among untreated than among treated cases. For these "superadded streptococcal infections" Kling and Widfelt recommended the use of a suitable antistreptococcal serum. Practically the same effects were obtained irrespective of whether the blood came from a mild, a moderately severe or a severe case of scarlet fever, or whether it was taken during the fourth, fifth, sixth or seventh week of the disease. On the other hand, early treatment gave better results than late treatment. Of the cases treated during the first three days of the disease, 90 per cent. recovered, while of 10 patients treated on the sixth day, 5 died. The total mortality in the epidemic in untreated cases was 70.3 per cent.,

while the treated cases gave 17.7 per cent. mortality. The early mortality for severe cases not treated with the convalescent serum was 50.5 per cent. against 10.5 per cent. for the treated cases. Late mortality in the severe, untreated and the treated cases showed respectively 19.8 per cent. and 7.3 per cent. of deaths.

Prognosis.—The prognosis of scarlet fever is largely dependent upon the clinical variety presented, and the complications that may ensue. Outside of these factors, prognosis in great measure also depends upon the character of a given epidemic and its locality, and the age and environment of the patient.

That the disease during the past fifty years has been much more benign than formerly is universally recognized. This is to some extent due to the more general custom of sending scarlet fever patients to hospitals, where, as a rule, they can receive better care than in the average private home from which the cases come, and partly also to the growing practice of administering diphtheria antitoxin to scarlet fever patients, inasmuch as the combination of the two diseases yields very high mortality figures.

With the use of immunization methods now in the process of development, scarlet fever, like diphtheria, bids fair to lose much of its hitherto menacing character.

The influence of *sex* on mortality is unimportant, although the death rate seems to be somewhat higher among males of all ages than among females. Infants, though rarely affected, show a relatively higher death rate than older children; the highest mortality figures occur during the first five years of life, but for children of all ages 90 per cent. of deaths from scarlet fever occur among those under ten years of age. The colored child has a better chance of recovering from scarlet fever than has the white child. Dublin gives a relative mortality of four to one among white and colored children, respectively. We find the death rate to be six times greater for the white children than for the colored ones.

As to *functional results*, except for the rare instances in which severe, and probably improperly treated, aural complications result in impairment or loss of hearing, there are no indications that scarlet fever—unlike typhoid fever—once overcome, leads to any permanent functional derangement or to a particular susceptibility to other infections, such as tuberculosis, etc.

Pathology.—The gross lesions of scarlet fever are few and much slighter than might be expected from the oftentimes severe character of the clinical features. The principal ones are a more or less marked acute dermatitis, and a catarrhal or inflammatory process of the mucous membrane of the mouth and throat. This process is seldom gangrenous or necrotic, and occurs only in the anginose and diphtheroid cases. It rarely involves the larynx. It, however, often extends to the middle ear and the nose; from the former it may spread to the mastoids, the meninges, the brain; and from the latter to the accessory sinuses, especially the antrum of Highmore. Congestion may also extend to the esophagus, while involvement of the cervical lymph glands and the surrounding tissue may lead to cell hyperplasia, suppuration and gangrene.

The skin eruption, which sometimes covers the mucous membrane of the mouth and throat, is not seen after death. The one constant feature which is found at autopsy in all cases of scarlet fever is hyperplasia of all the lymphoid tissues. Other important lesions, due mainly to complications of the disease, are degeneration of the parenchymatous

organs, the liver, the kidney, and, to a less degree, the muscles of the heart which often is dilated and hypertrophied as a result both of the scarlatinal poison and the kidney involvement. In the severely toxic cases with wild delirium there is edema of the brain and evidence of meningeal inflammation; splenic tumor is also sometimes seen. In these severe cases the rapidly fatal course is no doubt due to the overwhelming toxicity of the causative agent of the disease, although other contributing factors, such as status lymphaticus, are often noted postmortem.

CIRCULATORY SYSTEM.—The *changes in the heart* are mainly a fatty degeneration of the muscles. Recent studies, however, have shown marked pathological changes in the heart ganglia, to which the cardiac paralysis in the severely toxic and rapidly fatal cases is attributed. In a special study of the myocardium and the heart ganglia in scarlet fever, Stegeman found round-cell infiltration in the stroma of the heart ganglia constantly present, even from the first day of the disease, its intensity being dependent on the severity (complications) and duration of the illness. Fatty degeneration and necrosis of the nerve-cells are likewise present from the first day of the scarlatina. Nissl bodies, in the severely toxic cases with early death, were markedly diminished in size and number when compared to the more prolonged cases. In the latter (septic and pyemic cases), where death ensued after the fifth and up to the thirty-eighth day, the myocardium showed parenchymatous and fatty degeneration as well as necrosis.

According to the studies of Klein and of Pearee (cited by Welch and Schamberg), the *changes in the lymphatic glands* consist of hyaline degeneration in the center of the gland in which are found large cells, some resembling giant cells and others having transparent vesicular nuclei. The sinuses are dilated and contain many endothelial cells lying free in the lumina, as well as large and small cells with one or more transparent nuclei, some of the cells showing phagocytic properties. The blood-vessels are congested, occasionally also showing signs of hemorrhage.

In the severely toxic form of scarlet fever in which the necrotic process in the nasopharyngeal region is the dominant feature, the streptococcus is recovered from the tissues as well as from cultures of the accumulations in the mucous membrane, the submucous tissues and the regional lymph glands. It is conceivable that the organism not only sends its toxic products from the throat into the blood stream, but that it may also penetrate the vessels and from these enter all other organs which not infrequently develop pyemic processes in which pure cultures of streptococci are found to reside, and which add to the pathology of scarlet fever. Such conditions comprise multiple joint suppurations, abscesses of the peri-articular tissues, muscle abscesses, subcutaneous abscess formation, purulent disease of the serous coatings (pericarditis, endocarditis, peritonitis), etc., all of which have been considered under the complications of scarlet fever.

Pearee, to whom we owe much of our knowledge of the morbid anatomy of scarlet fever, describes the changes in the *tongue* as dilatation of the papillary blood-vessels and lymphatics and leukocytic infiltration of the epithelial layers, especially over the papillae and among the blood-vessels. He regards the process as an inflammatory one, probably due to positive chemotaxis excited by the scarlet fever toxin present in the tissues or by the products of its action on the superficial epithelium.

RESPIRATORY SYSTEM.—The lesions of the pulmonary region, in the

cases where it is involved in scarlet fever, are usually those of a bronchopneumonia affecting one or both sides. That they are due to the scarlatinal infection is seen from the presence of streptococcus associated with staphylococcus aureus. The pleura likewise may be attacked by the streptococcic infection; the route of infection from the respiratory passages to the pleura has been traced by Simonin by areas of hepatization of the tissues.

DIGESTIVE SYSTEM.—*Gastro-intestinal Tract.*—Involvement of the gastro-intestinal tract is not one of the features of scarlet fever, although in rare instances the necrotic process from the throat has been known to extend along the esophagus and into the stomach, causing more or less pronounced destruction of the mucous membrane along its route. Involvement of the intestinal mucosa is usually limited to catarrhal enteritis.

Liver.—Hepatic enlargement is one of the most constant gross findings in scarlet fever. The icteric discoloration of the skin and the urobilinuria, often seen at the height of the exanthem, are undoubtedly due to disturbed hepatic function. Histological studies demonstrate a constant, more or less marked small-cell infiltration of the connective tissue extending to the parenchyma, and in some rare instances, necrosis. The latter may, however, undergo regeneration. Interstitial hepatitis, lymphatic neoplasms and cirrhosis have also been observed.

Spleen.—The changes in the spleen are generally described as consisting either of enlargement of the splenic pulp or enlargement of the malpighian bodies without increase in the size of the pulp, which in such instances has a firm, smooth but not tense capsule. The malpighian bodies appear as prominent grayish-white areas against a dark, reddish background. When the pulp is enlarged it is soft, and the malpighian bodies are indistinct. In stained microscopic sections their centers are pale, while the periphery is deeply stained and contains many plasma cells. This infiltration of plasma is also observed in all parts of the pulp within the blood-vessels and along the trabeculae. The center of the malpighian bodies consists of more or less fused phagocytic cells—masses of endothelial cells from the lymph nodules.

URINARY SYSTEM.—The kidneys, of course, occupy a very important place in the pathology of scarlet fever. The anatomical changes in scarlatinal kidney disease are those of an interstitial and a glomerular nephritis. In the former the kidneys are more or less swollen and their superficial surfaces dotted with red spots; in cross section a striated redness of the dilated cortex is seen, the markings of which are ordinarily obscured. Microscopically there is an accumulation of lymphocytes, the density of which has a direct bearing on the degree of leukocytic infiltration and consequent structural destruction. These changes may be present early in scarlet fever, especially in the septic cases, without producing any clinical manifestations, but when they are diffuse the symptoms are correspondingly intense, and in cases where the entire kidney is affected death may ensue. The glomeruli themselves remain intact. In fact, nephritic foci may persist beyond the third week of scarlet fever and clinically present no symptoms of nephritis without glomerular involvement. Escherich and Schick suggest that the cases so often reported of slight clinical symptoms and marked renal changes probably belong to this class.

In the glomerular nephritis, generally regarded as typical of scarla-

final nephritis, the kidneys, except for a slight edema, appear normal at a first glance. It is only upon careful examination that the glomeruli are seen on the cut surface, to which they lend a granular appearance. All the glomeruli are affected, but other changes may be slight and unimportant or altogether absent.

The first visible signs of pathological changes are thickening of the walls and increase in endothelial nuclei of the tubules. This is followed later by leukocytic infiltration and displacement of the lumen. The powerful rush of blood to the glomeruli produced by a simultaneous rise in blood-pressure and cardiac enlargement causes distention of the glomeruli. The restoration of the patency of the latter is part of the healing process, the blood in the urine being part of the phenomenon, its amount serving as a gauge of the progress of the healing. Sometimes thrombosis of the capillaries causes new obstruction, with death from cardiac paralysis as a possible result. In rare instances diffuse infiltration may lead to loss of function of the glomeruli, the formation of adhesions and to epithelial proliferation with chronic nephritis as a possibility.

Escherick and Schick distinguish between *septic scarlatinal nephritis* and *glomerular nephritis*. The septic type forms a part of the general septic process and can be expected to occur where the streptococic infection causes severe necrotic pharyngeal changes. The degree of anatomical modification greatly exceeds that of the clinical manifestations. The urine contains more or less albumin and nephritic sediment, but blood is not visible macroscopically, nor is the urinary output much diminished. While the streptococcus is properly regarded as the etiological factor in this form of nephritis, the histology of glomerular nephritis does not justify such a supposition, even though streptococci have been recovered from the urine in the latter. Escherick and Schick consider the glomerular nephritis to be a so-called toxic or excretory nephritis. It is entirely possible, they believe, that streptococci present in the blood in late stages of scarlet fever may pass through the diseased kidneys into the urine without contributing to the pathological process in the kidneys. This bacteriuria raises the interesting question whether or not other microorganisms, as well as streptococci, and particularly the streptococcus hemolyticus of scarlet fever, can leave the body by way of the urinary canals, and suggests the possibility that, as in typhoid fever, the urine of scarlet fever may play a part in the spread of the disease. While scattered reports in literature indicate such a possible infectivity of the urine, there as yet is no accurate demonstration of the fact.

ENDOCRINE GLANDS.—The endocrine glands are not generally considered as contributing to the pathology of scarlet fever, but French writers, more especially Hutinel and others, have recently insisted upon the importance of adrenal and pancreatic insufficiency in the syndrome of scarlet fever, and in interesting histological studies have demonstrated cellular and glandular changes on which they base their claim. Hutinel has also observed isolated instances of slight modification of the thyroid gland and also one case in which changes in the hypophysis were present. Although these changes were always associated with modifications in the suprarenal gland, it is conceivable, he thinks, that they may occur independently.

OSSEOUS AND NERVOUS SYSTEMS.—The *bone marrow* in septic cases sometimes is found to contain small collections of round-cells and minute

streptococcic foci, the latter being partly intravascular and partly free in the tissue. Jochmann claims, in such instances, to have found streptococci present in the *spinal cord*.

BLOOD.—The chief interest in the blood changes in scarlet fever centers around the leukocytosis and inclusion bodies. Leukocytosis is already noticeable during the incubation period and reaches its maximum at the height of the disease. In mild cases it ranges from 17,000 to 34,000; 14,000 to 40,000 in severe cases. Differential count shows also a change in the eosinophils. They are either decreased or disappear at the onset of the fever, rising later and remaining high until convalescence sets in.

The chief value of the blood-count is a diagnostic one. Increase in leukocytes in a suspected case of scarlet fever with an ill-defined or aberrant rash will serve to distinguish it from measles in which leukocytosis is not present; or when a person has been exposed to the disease, leukocytosis during a possible incubation period will strengthen the suspicion of the existence of scarlet fever. In doubtful cases well-marked eosinophilia on the third or fourth day will also be of diagnostic value.

SKIN.—With few exceptions investigators interpret the skin changes in scarlet fever as the result of an inflammatory process. According to the researches of Pearce, the changes are not pronounced until after the third day of the disease; *i.e.*, from the fifth to the tenth day he was able to note marked infiltration of the epithelium and the connective tissue with polymorphonuclear leukocytes. The lymphatics were much dilated and also contained polynuclear leukocytes. The leukocytic infiltration had disappeared from specimens taken on the twelfth day of the disease.

Rach, in a more recent study of the histology of the skin in scarlet fever, describes the process as an acute inflammation with an exudate which is at times serous and at others multicellular and hemorrhagic, the predominating cells being polymorphonuclear and neutrophile leukocytes. The inflammation is manifested in the skin by more or less dense foci (individual punctæ or efflorescences). The favorite site of the punctæ appears to be around the orifices of the hair follicles, but they often protrude beyond that area, either owing to edema of the underlying cutis or to accumulations of the exudate in the epidermis. This follicular swelling thus represents the anatomical basis for the typical scarlatinal minute papulous punctæ.

The changes were observed in various stages with gradual transition from one to another. The first stage is that of exudation in which (a) the exudate leaves the vessels and enters the upper layer of the cutis, and (b) enters the epidermis where it accumulates and gives rise to the microscopic vesicles, which often are also visible to the naked eye. The second stage is desquamation with the shedding of incompletely hardened (parakeratosis) particles of epidermis.

The fact that the efflorescences in various stages were seen side by side indicates that the exanthem develops at successive stages.

Historical Summary.—The works of Galen, Rhazes and other ancient writers contain various descriptions of a disease with throat symptoms and a diffuse red eruption suggesting scarlatina, but not until the sixteenth century was the disorder differentiated from measles by Ingrassias, of Naples. The first accounts of what appears unmistakably to be scarlatina are those of Daniel Sennert, of Wittenberg, and his son-in-law, Michael Doerring (about 1625). They give us the typical picture of

scarlatina, the rash, desquamation, joint pains, anasarca and delirium. Sydenham (in 1676), however, was the first to present a careful analysis of the disease with its medical characteristics and to give it the designation scarlatina or scarlet fever. He also differentiated it from measles, with which it was constantly being confused. The epidemic which gave Sydenham the opportunity for studying scarlet fever in large numbers was evidently a mild one, since he believed the disorder scarcely deserved to be considered a disease. But he was destined to change this belief fifteen years later when an epidemic of unusual malignancy, described by Mortons, broke out in England. Huxham (1740) appears to have been the first to call attention to the importance of angina in the symptom-complex of scarlatina.

The disease was common in Europe during the eighteenth century and from the middle of that era spread over both hemispheres. According to Caiger, it first appeared in the North American Colonies in 1735, spreading over New England, reaching New York in 1746, thence extending to the coast states. By 1791 it made its appearance in the interior, reaching Canada and the Northern states during the early part of the nineteenth century. South America was not invaded until about 1830, and since then the disease has appeared often and at times in severe epidemic form, in nearly all of the countries of that part of the continent. During the middle of the nineteenth century scarlatina was reported from Polynesia, New Zealand, Tasmania, Australia and in distant Greenland and Iceland (in 1827 in the latter).

The disease appears irregularly in epidemics of greater or less virulence, often extending over a period of years; in large centers of civilization, however, it is always more or less prevalent.

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CHAPTER XIII

RUBEOLA

(*Measles*)

By WILLIAM A. JENKINS, A.M., M.D.

Definition, p. 281—Etiology, p. 281—Symptomatology, p. 283—Incubation, p. 283—Invasion, p. 284—Eruption, p. 286—Desquamation, p. 288—Laboratory findings, p. 288—Diagnosis, p. 288—Association with other diseases, p. 289—Complications, p. 289—Sequelæ, p. 290—Treatment, p. 291—Prophylaxis, p. 291—Curative treatment, p. 292—Prognosis, p. 298—Pathology, p. 299—History, p. 300.

Definition.—Rubeola is an acute infectious, readily transmissible disease of unknown origin, characterized clinically by a well-marked catarrhal process of the mucosa of the upper air passages and a characteristic exanthem.

Etiology.—**PREDISPOSING CAUSES.**—Any constitutional defect, any disease process or pathologic change which tends to lower the individual resistance constitutes a predisposing factor; likewise any environmental factor which would fall below what would be considered the standard would be classed in the same category. Exposures to cold, the race, sex, soil, altitude, climatic considerations and seasonal changes exert very little influence in this disease.

As to age, the disease is almost unknown under six or eight months (there is very little chance for outside exposure during the nursing period). An infant may be born with measles, the eruption showing on the body at the time of birth, the condition being transmitted through the placental circulation, the mother having had it during the later weeks of pregnancy.

From two to twelve or fifteen years of age is the commonest period for the appearance of measles. From twenty to forty years the disease is fairly common only. Measles is uncommon in old age. (This may be partly explained by the fact that in many instances the individual has had the disease in childhood.)

Previous Attacks.—It is quite possible that an individual may have a second or possibly even a third attack of measles. The observers whose opinions are most worthy of consideration are agreed on this statement. It is not, however, at all common. As a rule, one attack of true measles confers immunity for life, and it is certain that very many of the reported cases of second and third attacks were simply mistaken diagnoses. Either the individual had a simple attack of urticaria, erythema, an attack of rubella (German measles) or, as occasionally

happens, some fugitive skin irritation or a drug eruption was carelessly spoken of as an attack of mild measles.

Panum, Rosenstein, Willand and other men who have paid very close attention to the exanthemata and have had a very rich experience state that they have never seen a second infection of true measles.

EXCITING CAUSES.—As was stated in the definition, measles is a disease of unknown origin, the special organism never having been isolated. Extensive examinations of the blood, tissues, secretions and excretions have been made. Microscopical examinations and cultural experiments have been carried out by experts under the most rigid and technical scientific requirements. The results were negative in every instance. The causative organisms are found in the blood. We have conclusive proof of this in the authentic, recorded cases of experimental inoculation, furnished in the literature of the subject.

Inoculation was first attempted at the direct suggestions of Munro, at Edinburgh, in 1758. The method was briefly as follows: Small superficial cuts were made across the measles spots in a selected portion of the body, the subject having a typical case of measles. Clean, soft cloths were placed in contact with the above-mentioned cuts and were allowed to become soaked with the exuding material. Then, a series of small cuts or openings in the skin were made on the arms of healthy individuals who had never had measles, and these soaked cloths were now loosely bound over the cuts for two or three days. Measles usually developed promptly, according to these observers. Cloths thus soaked retained their infectious possibilities for about ten days. Work of this character was carried out in Italy, England and the United States of America, some observers making as many as a thousand inoculations. The above experiments demonstrate that the disease is a transmissible one, that experimental inoculation is possible, and that the specific organism is present in the blood of the infected individual.

Experimental inoculations were successfully made also with the discharges from the mucous membranes of the upper air-passages; in fact, speaking from the standpoint of the experimental production of the disease, this proved to be the surest and easiest way, and it accords with our present-day conception of the chief method of transmission of this disease from one individual to another, namely, the secretions from the upper air-passages. These early investigators, in their inoculative experiments, gathered the fresh secretions from the upper air-passages of a known case of measles and placed them in contact with the upper air-passages of healthy individuals; the disease developed promptly in from eight to ten days. Contrary to statements of some observers, the consensus of opinion seems to be that the epidermal scales and tears do not contain the causative organism, as the inoculative experiments recorded along these lines were always negative or doubtful.

Modes of Conveyance.—In the great majority of instances this disease is transmitted by a direct or contact infection. There is no doubt that its chief method of transmission is by means of the secretions of the upper air-passages. Therefore, every object or article which has

in any way come in contact with a case of measles has been exposed to contamination from these secretions and may therefore carry the disease. For example, clothing, playthings, handkerchiefs, towels, fomites of any sort may be responsible for transmitting the disease. It is to be remembered, however, that the organism is not supposed to live on contaminated articles mentioned above longer than ten days. Individuals coming into the room and coming into direct contact with the sick individual may carry the specific organism of the disease on their persons and their clothing.

To illustrate, we have records of a healthy person, e. g., a physician visiting and examining a case of measles in an infected locality and then traveling for a considerable distance into an isolated community and spending the night with a family. After fourteen days measles broke out in this household. Later investigation proved the above means or route to have been the only possible explanation of the appearance of the disease.

Symptomatology.—For the sake of convenience and discussion, it is customary to divide the subject into periods: namely, (1) Incubation; (2) Invasion; (3) Eruption; (4) Desquamation.

(1) INCUBATION.—The incubative or hatching period embraces the interval between the implantation of the causative agent on the selective tissue of the host and the manifestation of symptoms. This definition will hold good for the incubative period in all infectious diseases, whatever the location or character of the infection may be. Much needless confusion has arisen in medical literature from an improper conception, on the part of medical authors, of the true limits of this period. Likewise, this same confusion exists with reference to what is going on in the body of the infected individual during this period.

Many authors in their descriptions of the whole group of the exanthematous diseases conceive the incubative period as lasting from the time the organism gains entrance into the system until the first appearance of the eruption (exanthem). Such a conception is manifestly incorrect, as it would include the invasional or prodromal symptoms as part and parcel of the incubative period. Again, in cases of known exposure (the exact time and the attending circumstances having been carefully noted, afterwards proven by the prompt appearance of the disease) it is all too common for some over-zealous observers to seize upon any small happening, e.g., malaise, headache, slight fever (all fugitive in character), or, in fact, any physiological perturbation whatsoever, and dignify the condition by speaking of it as a symptom of the incubative interval, when as a matter of fact the symptom in question was merely a coincidence and might just as well have happened to the individual had he never been exposed to an infection.

When disease-producing microorganisms (animal or vegetable)—infectious agents, in other words—gain entrance into the human host, they must first find a part or tissue of the body where conditions are suitable to their growth and multiplication, and when they have found such a location, the incubation may be said to have begun, and not

until then. Now, after the organism is appropriately located, a certain amount of time is necessary before the organism can prepare or elaborate a sufficient amount of poison to react on the fluids and tissues of the body and thus produce definite symptoms (which is the name that we give to such reactions). Scientifically speaking, the above comprises the true incubative interval. This period is a variable one and depends on the one hand on the amount, character or kind and virulence of the invading organisms, and, on the other, on the particular type of tissue invaded. Direct inoculations, experimental or accidental, always appear to shorten the incubative interval, because in direct inoculation, the microörganism is placed at once in contact with its selective tissue and under the most favorable conditions, consequently growth immediately begins (we skip the pre-incubative stage).

Now, when an infection is contracted in the ordinary clinical manner, the organism has gained entrance into the body, but it may be detained in any unfavorable location for quite an appreciable period of time (the pre-incubative interval), before it is finally transported to its particular selective tissue, where growth readily begins. From the foregoing considerations, then, we can readily see that the incubative interval is, clinically speaking, a quiescent period and from the very nature of the case there can be no symptoms in this period.

Perhaps in the future, when the intricacies of the science of immunology are better understood and the discovery of new and improved methods of investigation have enabled us to scrutinize more deeply the phenomena of infections, certain serological or cytological phenomena may be developed which may be said to constitute symptoms of the incubative interval. At the present time we have no such advanced methods or facts. The incubative period of measles is, therefore, void of symptoms. From the standpoint of time, the incubative interval of this disease may be said to be from ten to fourteen days. Fourteen days seem to be the period of choice with most authors.

(2) *INVASION*.—When the exciting cause (microörganism) of measles, after implantation on its selective tissue, has elaborated sufficient poison to react on the tissue-cells and fluids of the body, thus causing physiological perturbation (symptoms), we are confronted by the phenomena or symptoms of invasion. The period of invasion (sometimes spoken of as the prodromal stage) begins rather suddenly or abruptly and lasts, as a rule, three or four days (exceptionally five or six days or even longer). The symptoms manifesting themselves during this period may be classified or grouped under three heads, viz.: (a) general or systemic disturbances, (b) catarrhal symptoms and (c) the symptoms of the enanthem.

(a) *General or Systemic Disturbances*.—We often notice that there is a coated tongue with loss of appetite. The child complains of being "sick at the stomach," with even nausea and vomiting in some cases. The patient exhibits a "desire to lie around" and does not feel like doing anything—general malaise as we physicians call it. Headache, chiefly frontal in character, is commonly exhibited. Some fever is

almost universally present and in typical cases the behavior or curve of the fever is definitely characteristic. It begins with the other symptoms of onset and rises to a peak in twenty-four to forty-eight hours (usually about the second day). It then remits to rise again to a second acme or high point before or just at the full flush of the exanthem. Careful observations compiled from our records of epidemics in child institutions, orphan asylums and the like enable us to verify the above, for under such circumstances we have competent nurses who may be taught to observe and record all symptoms from the most fugitive beginning prodromal symptoms up to the time the child is discharged.

This class of work has convinced clinicians that the fever curve of measles is prone to exhibit two peaks or high points, one occurring in the prodromal state (about its mid-point), the other during the height of the eruption. It is likewise a commonly accepted dictum that if we take a view of the entire febrile curve of the disease, we will note a tendency on the part of the fever to exhibit a slight morning remission and evening exacerbation.

Now and then we may have some enlargement of the lymphatic glands about the neck and under the jaw. This, however, is neither a characteristic nor a diagnostic feature. In certain severe and malignant epidemics, cases are occasionally seen which manifest very grave and alarming symptoms, even in this early period, the patient passing rapidly into a somnolent or typhoid-like state or even becoming comatose with great prostration supervening. It is to be understood, however, that the above, while it may possibly occur, is not in any sense to be considered as forming part and parcel of the typical syndrome of measles.

(b) *Catarrhal Symptoms*.—The catarrhal symptoms present themselves early. They are characteristic and are sufficiently well marked and constant to be of real diagnostic value. In the first few hours, there is a sense of fullness or a stuffy feeling about the nose; sneezing may be frequent. The throat feels dry and sore. Next the nasal secretions begin, the nose runs, the acrid secretions irritating or even excoriating the upper lip. The pharyngeal ring becomes reddened. Now we have a typical nasopharyngeal catarrh. At the same time a brassy cough (with or without hoarseness) appears. A mild type of bronchitis may be present at this stage.

The ocular conjunctiva begins to show evidence of irritation and inflammation. First the eyes hurt and feel as if there were particles of dust under the lids. The conjunctiva becomes reddened, photophobia develops. Secretion is increased; the lids tend to stick together in the morning and in extreme cases the eyes are swollen and blood-shot. The catarrhal symptoms persist throughout the prodromal period. They usually increase or become accentuated as the eruption or exanthem develops and likewise subside as the eruption subsides.

(c) *The Enanthem (the Internal Eruption)*.—Usually about the end of the second day of the invasional period, on the mucosa of the mouth and throat, there appears an eruption. The mucous membrane takes

on a dark-red color and is much engorged. Dark-red elevated spots appear from a pinpoint to a pea in size, most common and most typical about the pharyngeal ring, noticeable also on the roof and floor of the mouth, and to a lesser extent, on the mucous membrane of the lips and cheeks.

Very frequently we notice, on the mucosa of the roof and floor of the mouth and lips, another type of spots. They are most commonly found on the mucous membrane of the cheeks, about opposite the molar teeth. These spots are slightly elevated, of a dark-red color and are about the size of a pinhead, and the center of each spot is occupied by a minute, white or bluish-white speck. These are called Koplik's spots, so named after the physician who first called definite attention to them.* Koplik's spots are hard to distinguish unless one has a very strong light. Strong daylight is best. These spots are believed to be present in from 90 to 95 per cent. of cases. Many authors regard the spots as being of great diagnostic value. Still others of wide clinical experience do not regard the Koplik's spots as possessing any especial value from the standpoint of diagnosis, claiming even to have found them in other of the exanthematous diseases.

The finding of typical *Koplik's spots* a day or two before the eruption, especially in the presence of marked catarrhal symptoms, strengthens the possibility of a pre-eruptive diagnosis. This is particularly true if we are dealing with epidemics, if we have knowledge of the diseases that are prevalent in given areas, or if we know that there has been a definite exposure. In all isolated, sporadic cases, we are confronted by a very different proposition. By way of conclusion, then, we may say that the finding of Koplik's spots adds another sign to the symptom group. It is another bit of evidence, another link in the chain, and is of value to just that extent. The finding of the spots could never make the diagnosis positive. On the other hand, the absence of the spots could never exclude the diagnosis.

Their time of greatest value is early in the disease, as they appear most promptly with the enanthem and tend to change character and fade as the eruption comes out.

We should, perhaps, make mention of the fact that the enanthem occasionally spreads by continuity of structures into the larynx, sometimes producing an alarming edema and even invading the mucous membrane of the bronchial tubes. Other observers have reported cases of involvement of the mucous membrane of the stomach and duodenum.

The literature of the subject likewise furnishes reports of a few instances of involvement of the mucosa of the rectum and the vulva. Care should always be exercised to avoid mistaking thrush, and aphthous stomatitis for the Koplik's spots, as either of these conditions may occur as an early complication. A consideration of their individual distribution and character should, however, prevent error.

(3) ERUPTION.—In typical cases, the eruption is prone to appear on the fourth day (it can appear earlier or one, two or several days

* See article by Koplik, *Archives of Pediatrics*, Dec., 1896.

later). The rash appears first as small red spots (macular, quickly becoming elevated or papular) on the forehead and sides of the face about the cheek bones, often showing behind the ears. Then the neck, chest and trunk are involved, likewise the arms and hands, legs and feet are invaded by the eruption. The palms of the hands and the soles of the feet may be red and injected, the eruption rarely becoming papular in these locations; the same may be said of the hairy scalp.

Usually the rash spreads rapidly, often covering the entire body in 24 hours; again it may take two or three days. The small red papules quickly increase in size and sometimes coalesce. The individual spots may vary in size from a pinhead to a common bean. The color commonly deepens and may be purplish or violaceous. The spots occur in irregular patches, splotches or clumps over the surface of the body. The old writers speak of the patches as having a crescent shape.

The eruption may be scattered thinly over the body or it may thickly stud the entire body. The eruption persists for some days, about four or five days or a week on the average. Then it quickly fades. The fading process follows the order of the appearance of the spots, head first, then neck and chest, body, legs and arms. The deep purple of the spots fades and they tend to have a brownish shade; slight pigmentation remains for two or three weeks.

Variations of the Rash.—Reliable authors have reported cases (observed in epidemics) without a rash. The rash is occasionally very slight, lasting only a day or so. It may appear on only a small part of the body. On the other hand, it may be unusually prolonged, lasting two weeks. In very severe and fatal forms of the disease, the rash may be hemorrhagic (black measles). The rash may appear to be under the skin, not coming to the surface well. Heat and warmth tend to bring out the eruption, while exposure to the cold or even chilling may serve to retard its appearance.

The character of the eruption is modified somewhat by various pathologic states of the skin, namely, eczema, psoriasis, erythema, etc. Relapses of the eruption are recognized as possibilities. They have been observed and recorded occasionally by reliable observers.

The progress of the other symptoms during the eruption are as follows:

Fever.—The fever reaches a second peak or high point a few hours before or at the time of the full bloom of the eruption. Then it subsides, usually rather gradually, for two or three days, occasionally rather quickly, like a crisis. A big rise in temperature after the rash has been out several days most likely means a complication. A few hours before the eruption, even, the face looks puffed and is slightly red and has a rather mottled appearance. The red color of the eruption deepens and takes on a purplish shade and becomes markedly papular or elevated to the touch. The legs and forearms show the spots last.

Catarrhal Symptoms.—The catarrhal symptoms of the invasional stage are still present and increase. The coryza increases. There is an

irritating discharge from the nose. Photophobia is intense. The eyes are likely to be blood-shot. The lids tend to stick together. The voice may be hoarse, with a brassy, troublesome cough, with mucous râles present over the chest. A thick tenacious mucus is expectorated. It is the rule for the catarrhal symptoms to subside as the eruption disappears. Their persistence would suggest a complication. The tongue is moist and coated usually with a white fur. The appetite is poor, there is present some nausea or vomiting and occasionally diarrhea.

(4) DESQUAMATION.—The subsidence or disappearance of the eruption marks the beginning of the desquamation period (the *convalescent state*, as it is often called). In a given case, if there are no complications, the patient improves rapidly, appetite returns, thirst disappears, photophobia is gone, the catarrhal symptoms gradually leave, although slight cough, bronchitis and soreness of the throat may persist. A slight branny scaling of the skin takes place and in ten days or two weeks the patient is well. There is, however, a marked susceptibility to external influences in this period. They should be examined and supervised throughout the period.

LABORATORY FINDINGS.—The laboratories are well-nigh useless to us in this disease. Some authors claim a slight leukocytosis in the incubative period and the first part of the invasion, stating that before or as the eruption comes out, the leukocytosis disappears, and we may have a leukopenia. They also state that the polymorphonuclear leukocytes are liable to be increased during the attack, dropping back to the normal as defervescence takes place. The blood findings are neither characteristic nor dependable. Albuminuria is a common finding and the same may be said concerning an occasional cast.

Diagnosis.—The diagnosis is based chiefly on the catarrhal symptoms and the exanthem. A characteristic exanthem is always the strongest point in the diagnosis of this disease. Second in value is the character and behavior of the catarrhal symptoms, plus the enanthem, with the accompanying spots of Koplik. The average case of measles, after the appearance of the eruption, is not likely to be mistaken for anything else. Before the eruption appears, it is always hazardous and difficult, and many times impossible, to make a diagnosis. Many shrewd clinicians always keep themselves posted as to what infectious diseases are prevalent in certain areas or localities, likewise they keep themselves posted regarding the matter of possible exposures on the part of their patients—and they use this knowledge in drawing conclusions.

In isolated, sporadic cases, where no infection, contact or exposure can be traced, where the case seems to come out of a clear sky, diagnostic difficulties arise. A case fulfilling the conditions mentioned above can never be diagnosed positively in the pre-eruptive state. Many cases of influenza, in the early stages, present a picture very like that of the prodromal state of measles. In the literature of the subject, we find instances where physicians have experienced difficulty in differentiating this disease from typhoid and typhus fever, etc., in the early stages. The other exanthematous diseases also are a common source of diffi-

culty in the early stage. Drug eruptions and erythemata are sometimes confusing.

The diagnosis should never be made on one feature alone. The case should be considered in its entirety. In doubtful cases, it is always best to wait for the appearance of the eruption before coming to a definite decision.

Association with Other Diseases.—The association of other diseases with measles (a double infection), which occasionally happens, always tends to increase our diagnostic difficulties as well as increase the danger to the patient. Among those diseases mentioned as having occurred rather commonly in connection with measles, we have the following: variola, varicella, vaccinia, scarlatina, rubella, typhoid fever, diphtheria, whooping cough, etc. The double infection is an accidental one. There is positively no relationship existing between the two diseases. No specific chemical or biological affinity can be said to exist. The laws or rules governing the successful implantation of one infection apply equally to the other, and in no way whatsoever does the one depend upon the other for its presence. The relationship is purely accidental or incidental.

Complications.—When any typical symptom of measles gets to be sufficiently severe, or accentuated, as to occupy a position of importance in the progress of the case, that symptom may be spoken of as constituting a complication. Likewise when any morbid process or intercurrent disease implants itself on the individual, when that individual is already the subject of an attack of measles, the resultant process may be said to constitute a complication.

THE SKIN.—Miliary vesicles may appear among the papules. Simple erythemata or urticarial processes may occur at any time throughout the disease. Secondary infections of the papules with microorganisms, commonly staphylococci, may rarely cause a few pustules to appear. Chronic skin eruptions, if present, will influence or modify the character of the eruption. Among the skin diseases which occasionally complicate measles may be mentioned eczema, psoriasis, erythema, impetigo, pemphigus, etc.

THE EYE.—An intense conjunctivitis may appear; edema of the lids is occasionally present. Keratitis and iritis are likely to occur in scrofulous children. Corneal ulcerations, phlyctenular ulcerations and granular lids are among the rare complications. The inflammatory process may extend and plug the lacrimal gland. Hordeolum or sty and blepharitis marginalis may be present.

THE NOSE.—Inflammations and secondary infections of the nasal mucosa occasionally appear. The pharyngeal ring is commonly inflamed. The eustachian tube may become plugged and inflamed, fail to drain properly and produce by extension an inflammation of the middle ear.

THE EAR.—Simple catarrhal processes of the eustachian tube are quite common. If the patient has enlarged tonsils and adenoids, the likelihood is much increased. The eustachian tube does not drain well,

the inflammation extends up into the middle ear and the drum may rupture. We have a typical case of otitis media. Measles, according to the statistics, causes from 2 to 10 per cent. of the diseases of the ear and fully 10 per cent. of all running ears are due to measles. Ear involvements, therefore, are very common, and through this channel the meninges and even the brain substance may be involved.

THE AIR-PASSAGES.—Simple laryngitis, edema of the larynx and tracheobronchitis are encountered frequently. Pneumonia, especially in poor, impoverished, debilitated children, is one of the commonest, as well as the ugliest, complications with which we have to deal. The type is most commonly lobular, although the lobar type may occur. Pleurisy, empyema and even tuberculosis occasionally present themselves.

THE GASTRO-INTESTINAL TRACT.—The frequency of the different types of stomatitis has already been mentioned. Diarrhea is occasionally seen in epidemics and in severe cases, and even serous peritonitis has been described as occurring. It takes place by direct contiguity of structures from the inflamed and infiltrated walls of the intestinal tract.

THE KIDNEYS.—Albuminuria, a few casts and slight granular or cloudy swelling of the special structures of the kidney are quite frequently present, and occasionally true acute parenchymatous nephritis occurs.

THE HEART.—This organ is not commonly involved during the active stages of measles. If this organ is involved at all, the disease is most likely to occur as a sequel. An occasional tachycardia or other rhythmic disturbance may be present.

THE NERVOUS SYSTEM.—The nervous system is not ordinarily affected. Such disturbances as do occur are more of the nature of temporary or functional aberrations than otherwise. There are a few cases, however, in which meningitis, neuritis and brain substance involvement are encountered.

Frequently diphtheria and whooping-cough may be epidemic in the same locality with the disease under discussion, hence, either of these diseases may complicate measles.

Sequelæ.—A sequela (from *sequor*, meaning *to follow*) is a condition which arises or persists in the patient after the original infection has departed. The following items always exert an influence on the character, type and likelihood of appearance of sequelæ. First, external factors, e.g., dampness, unhygienic quarters, undue exposure during the early part of the disease in question, lack of treatment, improper treatment, etc. Second, internal (or personal) factors, e.g., all unfavorable influences existing in the constitution of the individual: (a) structural and functional defects or deficiencies; (b) disease taints (constitutional dyscrasias), e.g., scrofula, rickets, tuberculosis, chronic Bright's disease, etc.; (c) the character and virulence of the infectious organisms.

THE AIR-PASSAGES.—Any disease or condition which may appear as a complication may likewise appear as a sequel. This is true of all infectious diseases. In considering the sequelæ of measles, the air-passages easily take first rank. Laryngitis, bronchitis and pneumonia.

lobular or lobar, are quite common. A persistent harassing bronchitis is very prone to hang on and give us trouble. Lobular pneumonia is exceedingly frequent, especially in young, weak children, as stated above. Tubercular engraftment is always a possibility. Empyema occasionally appears.

THE EAR.—This organ is likely to furnish us with sequelæ. It has been stated that from 5 to 10 per cent. of our cases of permanent total deafness and middle ear disease (otitis media) with running ears, are directly traceable to an old attack of measles. All too frequently do we hear our patients say, "I have never heard well out of that ear since I had measles," or "That ear has been running off and on ever since I had measles."

THE KIDNEYS.—Almost every experienced clinician can from his case history files, produce a few records of acute Bright's disease which are definitely traceable back to a case of measles.

Practically all long and severe cases of measles will show a fair grade of anæmia on making a blood-count. In fact, it is quite within the range of possibility for almost any organ or tissue of the body to exhibit some impairment as a direct result of measles. For example, a young healthy boy 12 years of age developed measles. The family doctor was called when the eruption appeared. He prescribed, and left directions for the conduct of the case (the boy was not confined to bed). Just two weeks from the date of the doctor's visit to the case, he was called in again. He found the boy in bed, face and hands swollen, feet and legs swollen as high up as the knees. Pitting on pressure, anæmic mucous membranes, pain across the back, urine scant, red and cloudy. Examination of urine showed: Albumin abundant and hyalin and granular casts present. Diagnosis: acute parenchymatous nephritis, following measles. Inquiry disclosed the fact that this boy had been playing out in the grass in the lot adjacent to the house, in his bare feet after the dew had fallen. (The case occurred in the early summer.)

Treatment.—**PROPHYLAXIS.**—Our experience in epidemics teaches us that this disease is readily transmissible. We have every reason to believe that the causative agent is a filterable one. We feel quite sure that the disease is transmitted chiefly by the secretions from the nose, mouth and throat of the diseased individual. The organism is certainly in the blood, and may possibly be in the discharges from the gastrointestinal tract. These latter routes, however, do not furnish a very favorable opportunity for transmission from one individual to another. It is a fairly sure conclusion that it is chiefly the secretions of the nose, mouth and throat, as mentioned above, that we have to watch particularly.

The mode of transmission is most commonly direct from person to person. We know, however, that it is transmitted indirectly through articles, clothing or fomites, recently soiled with the secretions and discharges mentioned above. It is more than likely that the organisms do not live longer than about ten days on soiled articles or fomites.

The disease is communicable from the very earliest catarrhal symptoms (or even before that) until all traces of secretions have disappeared from the nose and throat.

With the above as a summation of our actual knowledge regarding the causative agent, its method of transmission and its period of communicability, we may formulate methods of control which will apply to the individual himself and likewise the community of which he is a member.

The methods commonly used to prevent the spread of acute infectious diseases are, in general, about the same everywhere. We can do no better than accept the rules laid down for the control of communicable diseases in the report of the American Public Health Association Committee on Standard Regulations, appointed in October, 1916. They are as follows:

"METHODS OF CONTROL

"(A) *The infected individual and his environment:*

"1. Recognition of the disease: Clinical symptoms. Special attention to rise of temperature. Koplik's spots and catarrhal symptoms in exposed individuals.

"2. Isolation: During period of communicability.

"3. Immunization: Blood serum taken from convalescents, when properly safeguarded and prepared, administered immediately or very shortly after exposure, has been proved to be of value in producing temporary passive immunity.

"4. Quarantine: Exclusion of exposed susceptible school children and teachers from school until 14 days from last exposure. This applies to exposure in the household. Exclusion of exposed susceptible children from all public gatherings for the same period.

"5. Concurrent disinfection: All articles soiled with the secretions of the nose and throat.

"6. Terminal disinfection: Thorough cleaning.

"(B) *General measures:*

"1. Daily examination of exposed children or other possibly exposed persons. This examination should include record of the body temperature. A non-immune exposed individual exhibiting a rise of temperature of 0.5° C. or more should be promptly isolated pending diagnosis.

"2. Schools should not be closed or classes discontinued where daily observation of the children by a physician or nurse is provided for.

"3. Education as to special danger of exposing young children to those exhibiting acute catarrhal symptoms of any kind."

CURATIVE TREATMENT.—Many cases of measles, even in epidemics, are so mild that little or no treatment is required. On the other hand,

a given case or an epidemic may be so severe that it will tax the therapeutic ingenuity of even the most experienced clinician and give us a very high mortality as an end-result. We can, therefore, give no rigid, definite, inflexible plan that will apply to all cases. Every case is a law unto itself.

We may as well acknowledge at the start that we have no specifics. **Sera, vaccines and immunizing agents** are (up to the present time, at least) useless in this disease. However, in the last few years blood serum taken from convalescents (when obtainable) has been used with encouraging results as an immunizing agent (passive, temporary immunity) and also as a therapeutic agent in the earlier phases of the disease. Of course great care must be taken to see that no transmissible disease is carried in the serum. A complete history, physical examination and Wassermann test should be carried out on the donor in every case before using the serum therapeutically. This phase of the subject is promising, but is not as yet on a commercial basis. The serum is therefore obtainable only under rare circumstances. We likewise have no **drug specifics**. The treatment is purely symptomatic. We shall take the subject up as follows: (1) *General management*, which shall include such measures as would apply to the average case; (2) *the treatment of special symptoms* (such as are prone to occur in severe cases).

(1) *General Management*.—The patient should be isolated in a suitable, comfortable room and a fairly even temperature maintained—from 65° to 70° F. (18.3° to 21.1° C.). Such arrangements should be made as will secure an adequate supply of **fresh air** for health and breathing purposes. (It is well to remember that fresh air need not necessarily be cold air.) The bed-clothing should be sufficient for warmth and comfort at all times. The old notion that the patient should be placed in a **darkened room**, for fear of injury to the eyes, is, of course, a mistake. If there is a high grade conjunctivitis present, with marked photophobia, make use of **colored glasses**, an eye shade or screen. These measures, however, are rarely necessary. It is best to have some fixed rule, applicable to all of the infectious exanthematous diseases, as regards **antiseptic precautions** as applied to the patient and all articles which are used by or come in contact with him. Also the method of caring for the discharges and emanations of the patient should come under the same rule. (*See Prophylaxis*.)

The *nurse* should exercise average care to prevent the possibility of carrying the disease to others. After examining a case of measles, the attending *physician* should always wash his hands and apply some alcohol, and before going to see another patient, he should always be out in the open for a while. In epidemic work in an institution, he should always wear a gown.

The erroneous notion that **water** is harmful in cases of measles is common among the laity. Water may be used freely, internally and externally. Every patient should receive a daily cleansing **bath** of warm soap suds and water, throughout the disease.

The **diet** in the average case of measles should be light, nutritious and easily digested. If the case is severe and gastro-intestinal symptoms are present, we must modify the diet to meet the requirements of the case. Plenty of fluids should be insisted on in all cases. Fruit juices and acidulated drinks are commonly acceptable to most patients, especially to children.

In the beginning of the attack, the bowels should be well cleaned out. **Calomel** is one of the best agents for this purpose. It may be used alone or combined with other suitable drugs. It may be given in a single dose or in broken doses, according to preference. The calomel should always be followed in a few hours by a dose of **oil** or a **saline**. Later an **enema** will usually suffice to keep the bowels open.

The upper air-passages should be kept open and clean by the frequent use of warmed simple antiseptics in the shape of **gargles** or **sprays**. Solutions containing **boric acid** [one dram (4.0 grams) to the pint], **carbolic acid** (5 drops to the ounce), and **bicarbonate of soda** [one dram (4.0 grams) to the pint], are good agents for the purpose.

The eyes should be washed out frequently with a warm **boric acid** solution or a normal saline solution. The presence of a cough will sometimes require a few doses of one of the standard (N. F. or U. S. P.) **anodyne expectorants**.

Many physicians are in the habit of administering a few moderate doses of **quinin** in the invasional or early eruptive stages, partly for its influence on the fever and partly, as they claim, to bring out the eruption. For the latter effect, many use **hot drinks**, e.g., hot lemonade, afterwards covering up the patient with **blankets**.

The writer recalls a justly celebrated pediatricist and medical teacher (long since dead) who always gave, as a routine measure throughout the disease, what he called his "**fever mixture**." It is as follows:

R

Sp. ætheris nitrosi..... ʒ ii (8 c.c.)

Potassii acetatis ʒ ii (8 gm.)

Aq. camphoræ

Liq. ammonii acetatis āā ʒ iss (45 c.c.)

M. Ft. Sol. Sig.: Teaspoonful in water every four hours (for a child under 5 years of age; above 5 years, increase the dose).

He claimed that this prescription was of great value in that it lowered the temperature and increased the elimination of waste by the kidney route and protected these organs at the same time.

To relieve the itching during the eruptive and desquamative stages, the body should be anointed daily (after the cleansing bath) with **carbolyzed vaselin**, 5 drops to the ounce. The period of convalescence should always be closely scrutinized for possible complications and sequelæ.

(2) *Treatment of Special Symptoms.—The Eyes.*—The eyes should always be kept clean. They should be washed out once or twice a day in the average case. A medicine dropper or a piece of absorbent cotton may be used, and plain, warm **water**, **normal saline solution** or **boric acid solution** (2 to 5 per cent. or even a saturated solution) applied. The saturated solution of boracic acid may be used every few hours if necessary. If pus is present, a solution of **argyrol** 10 per cent. to 15 per cent. should be dropped into the eyes, one or two drops every three or four hours, or according to indications. The margin of the **lids** may be **anointed with vaselin** before the child goes to sleep, to prevent sticking in severe cases.

Nose, Nasopharynx and Mouth.—**Cleanliness** and mild **antiseptics** are always indicated here: first, to inhibit the spread of the disease, as the secretions from these parts furnish the chief mode of the conveyance of the disease; second, and equally important, to prevent complications. Congestion furnishes mechanical difficulties, e.g., plugging of the eustachian tube, and it also favors the implantation of other organisms on the part (mixed infection). We readily see, then, how important it is to keep these parts clean. In mild cases, simple substances used as **gargles** and **sprays** (by means of an atomizer) are effective, e.g., **Dobell's solution**, **boric acid**, **sodium bicarbonate**, and various other mild antiseptic solutions.

Chlorazene (ehloramin), the new Dakin antiseptic, is being tried out rather extensively just now in epidemics in the army camps. It is used in a fresh 1-1,000 or 1-500 solution. It is to be freely sprayed into the nose, pharynx and throat every few hours. Pus on the tonsil or in the pharynx should be touched with **nitrate of silver** or other suitable agent.

The Bowels.—The bowels should be opened at the start with **calomel** and a **saline** as noted above. The indications after that would depend on the condition of the gastro-intestinal tract. If the tongue is clean and belly flat, an enema every other day would suffice. If the reverse of these conditions obtain, there can be no objection to the use of simple purgation throughout the disease as needed. Occasionally diarrhea appears. When this feature is present, the **diet** should be modified accordingly and the indicated remedies applied.

Fever.—A moderate degree of fever (103° or 104° F. [39.4° or 40° C.]) in this disease holds no especial significance. The temperature tends to reach a high point for only a very short time in most cases (from the last day or so of the prodromal stage until the eruption attains its maximum). **Hydrotherapy** is the best measure, by all odds, to combat the fever. Sponging with warm or tepid water is best. The full **bath** is left for extreme cases. Occasionally, just at the highest point of the fever, when the eruption is just blooming out and the child is restless, hot, coughing frequently and delirium seems near, it is legitimate to use the following prescription every two to four hours for two or three doses:

R

Codeinæ sulphatis grain $\frac{1}{8}$ (0.008 gram)

Caffeinæ citratis grain ss (0.032 gram)

Acetphenetidini grains iii (0.2 gram)

M. Ft. Capsulæ No. 1. Sig.: One capsule every 2 to 4 hours. This prescription is suitable for a child 5 years of age or older.

One or two doses is usually sufficient to quiet the patient, reduce the fever one or two degrees and allow him to fall asleep. **Coal tar derivatives** are never used as a routine measure. Prolonged temperature, after the eruption is all out, is usually due either to a complication or to severity of the disease. **Hydrotherapy, stimulants** and the proper attention to the complication present, would meet the demands of the case here.

The Ear.—Congestion and infiltration of the eustachian tube, and even earache, are quite common as special symptoms, and otitis media occurs very frequently. The best treatment is prevention. **Spraying the nose and throat**, relieving congestion and keeping the parts clean with **chlorazene** or other suitable antiseptics is best. If, in spite of these measures, there is some earache, dry heat may be tried, applied locally, or 5 per cent. carbolic acid in glycerin may be used. A few drops of this warmed and dropped into the ear every three or four hours is often efficacious.

If the earache increases in severity, inspect the drum membrane frequently by means of the head mirror and ear speculum. If the symptoms increase, with marked restlessness and rise of temperature, and if the drum membrane is tense, red and bulging, **incise** it in the lower posterior quadrant with a small thin-bladed bistoury (or paracentesis knife). After incision the pus, which flows out freely, should be wiped out every few hours with a soft pledget of cotton on an applicator. After the ear is cleaned, very gently wash out the ear with a small rubber syringe, using for the purpose a saturated solution of **boracic acid** in water. If the discharge should suddenly cease, the symptoms increase and the temperature jump up, with swelling and tenderness appearing behind the ear, the mastoid cells have likely become involved and a mastoid operation may be necessary.

The Skin.—Mention was made above of measures to bring out the eruption, e.g., **quinin** internally, **sinapism to the chest**, **hot drinks** and **blankets**, etc. While many of us use such measures infrequently or not at all, still we have no legitimate reasons for bitterly condemning them, so long as they do not injure the patient in any way, as it is commonly conceded by most clinicians that the case does best in which the eruption follows the type in both time and appearance. On the other hand, when the eruption is "driven in," as the laity say (inward measles), i.e., if it fails to come out, the cases are severe and complications are more likely to occur. For example, a young child is frequently brought to the outpatient clinic of a hospital in bad weather, in the

late prodromal stage of measles. (We make a tentative diagnosis at the time and the subsequent history of the case verifies it.) The eruption is tardy and imperfect and the clinical course of the disease is stormy. The intense itching is to be relieved by **bicarbonate of soda solutions**, one dram to the pint, or **carbolyzed vaselin**, 5 drops to the ounce. **Olive oil and oil of eucalyptus**, equal parts of each, applied daily, is good to relieve the itching and it likewise protects the skin during desquamation.

Air-Passages.—(a) *Laryngitis.*—This is a very common symptom in the early part of measles. It is very easily recognized by the croupy, stridulous character of the breathing and voice sounds. **Local applications** are very efficacious, **compresses**, either **hot or cold**. **Ice-water cloths** applied for a few minutes at a time is about the best method. **Inhalations** by means of a croup kettle and tent, of **compound tincture of benzoin and oil of eucalyptus** (of each a teaspoonful to the quart of water) are effective. Sprays may be used in the same way. When edema of the larynx is present, incorporate in the **spray** enough **adrenalin chlorid** to make a 1-20,000 solution and use it frequently. **Scarifying** or **local blood-letting** and even **intubation** are measures that are resorted to in extreme cases. If marked laryngitis should occur late in the disease, suspect diphtheria, and make a diligent search for it.

(b) *Bronchitis.*—Mild bronchitis with a dry, troublesome cough is often present as a prodromal symptom even. It may persist all the way through or appear at any stage of the attack, or even remain as a sequela after the attack is gone. The measures mentioned under laryngitis may be useful in the beginning of bronchitis. **Mustard paste**, or **cold compresses** alternating with heat, are useful at times. The cough which prevents rest and sleep must be controlled. The **sulphate** or **phosphate of codein** (grains $\frac{1}{16}$, $\frac{1}{8}$, or $\frac{1}{4}$, according to age) (grams 0.004, 0.008 or 0.016) is the most efficacious remedy.

If the child is old enough to expectorate, we use some of the simple **anodyne** and **sedative combinations** of the United States Pharmacopeia or National Formulary. A suitable dose of **codein** may be added to each dose of the above, if necessary. In the severer types in small children, say under three years, use strychnin sulphate (grains $\frac{1}{240}$), apomorphin hydrochlorid (grains $\frac{1}{120}$ every three or four hours, with nourishing food and support. If the patient is an adult or even an older child, use some of the stimulating expectorants, e.g., **syrup of hydriodic acid**, tablespoonful every four hours.

Minute amounts of **codein** may be added to any of the above, if the character of the cough demands it. A cough which drags along into convalescence and even increases in severity suggests tuberculosis or bronchopneumonia. Pneumonia, most commonly bronchopneumonia (occasionally the lobar type), may occur as a complication of measles. (For the treatment of either type, see articles on these diseases.)

The Kidneys.—Albumin is almost universally present in measles. In the adult, casts are frequently found also. True nephritis is a possibility at any time. The urine should be kept bland and abundant,

which can be accomplished by protecting the skin and administering plenty of **fluids**, especially water. The "fever mixture" prescription mentioned above is likewise useful. If nephritis arises, the appropriate treatment should be administered.

The Heart.—It is very uncommon for this organ to be involved by the disease under consideration. The average doctor practicing in a small place might go a lifetime and never see a case. The man of large experience will encounter a case occasionally. The order of frequency of involvement of the cardiac structures is as follows: first, endocarditis; second, pericarditis; third, myocarditis. (For treatment, *see* chapters on the Heart.)

The Nervous System.—The nervous manifestations most frequently encountered in measles are physiologic or functional in character. They are prone to occur at the acme of the disease or in severe cases. They are usually toxic manifestations, viz., irritation of nerve centers, produced by the presence of the toxins of the disease. The patient may be restless, highly nervous and tossing about, unable to sleep; occasionally he lapses into a muttering, incoherent, semidelirious state. **Hydrotherapy** properly applied usually relieves the above. Sometimes we make use of the **bromids** or the following prescription:

R
 Codeinæ sulphatis grain $\frac{1}{8}$ (0.008 gram)
 Caffeinæ citratis grain ss (0.032 gram)
 Acetphenetidini grain iii (0.2 gram)
 M. Ft. Capsulæ No. 1. Sig.: One every 2 to 4 hours
 for 2 or 3 doses. (This prescription is suitable
 for a child 5 yrs. of age or older.)

If coma is present, we have passed the above stage. The indications now are to support, stimulate and eliminate. Still more rarely we may have meningitis, neuritis, etc.

Prognosis.—In the average case the prognosis is good. However, in view of the special knowledge which physicians have of this disease, experience would teach us to make a reserved or guarded prognosis. By the laity, measles is regarded as a simple disease. Ordinarily they will say, expose the child and let him have the disease and be done with it. Our experience and the trend of the literature of the subject teach us to be more careful.

The mortality varies in different epidemics and the percentages given in the textbooks varies anywhere from 3 to 50 per cent. The prognosis has always been found to be grave when the disease is introduced for the first time into an isolated community.

To give us some true conception of the possibilities which this disease has as regards severity and mortality, it will be profitable for us to glance in a cursory way at the history and behavior of some of the great epidemics that have occurred in various parts of the world, especially in savage and uncivilized lands. (*See* writings of Hirsch.) An

epidemic occurred along the course of the Amazon River in 1749 and about 30,000 of the natives died. An epidemic occurred in the Hudson Bay district in 1846. Fully 50 per cent. of the native Indians had the disease severely and the mortality was high. In the Fiji Islands an epidemic occurred (described by Squire and Cruikshank) and 20,000 of the natives died, or about one-fourth of the population, roughly speaking. The disease was so severe that the natives fled in terror, deserting their own sick. Dysentery and congestion of the lungs of the severest forms existed as complications. According to the literature in some of the temporary hospitals in the vicinity of Paris (at the time of the Franco-Prussian war in 1871) the mortality from measles reached as high as 40 per cent. Exposure to the elements, unhygienic and unsanitary surroundings, the absence of proper care, food and medical attention, all played a part, of course, in determining the severity of the epidemics just referred to.

The above citations, selected almost at random from the exceedingly rich literature of the subject, serve in a very forceful way the purpose of impressing upon our minds the possibilities of measles under certain circumstances. Furthermore, physicians of the present generation who have had opportunities for wide experience in epidemic diseases will vouch for the statement that all the terrors and possibilities of measles are not confined to the literature of the past. The whole question, then, of the prognosis of measles is not so simple a proposition as it first appears to be on superficial examination; much depends upon the type and character of the individual epidemic. And perhaps still more depends upon the attendant circumstances which surround and accompany the epidemic.

The prognosis is likewise usually bad when this disease breaks out in army camps, barracks, prisons, etc. The presence of severe complications also raises the mortality percentage and adds to the gravity of the prognosis.

Pathology.—There is very little true pathology in this disease and that pertains chiefly to the skin and mucous membranes, and even this disappears when death occurs. The pathology, therefore, in most cases is that of the complications and sequelæ. There are, however, definite changes in the skin and mucous membranes. First, in the *skin*: There is present an hyperemic process of the superficial vessels of the skin with dilatation and extravasation of blood elements. A round-celled infiltration takes place, the sweat and sebaceous glands are dilated and their coils are packed with round cells. Small hemorrhages may occur and colloid degeneration of cells takes place, which is supposed to account for the appearance of the papillæ. There is likewise a catarrhal process of the *mucous membranes*, namely, hyperemia and extravasation of blood elements, denuded epithelium, the presence of blood-cells and possibly minute ulcerations. The so-called black or septic types of measles are most likely due to an hemolytic streptococcus. They are characterized by rapid blood disintegration, marked subcutaneous hemorrhages with such parenchymatous changes as are found

in grave septic processes, e.g., in the liver, spleen, kidneys and possibly even the heart.

History.—This disease comes to us out of the remote past; its origin reaches back perhaps into unknown antiquity. It occurred in epidemic form throughout Asia and Europe and was carried to America by the early settlers. Thence, by the streams of exploration, immigration and commerce, it spread to South America, Africa, Australia and even to the Islands of the Sea. The etymology of the term "measles" is not well nor definitely worked out. The following are some of the sources to which it is traced: From "Maselen" (Dutch); from "Masern" (German); from "masura" (Sanskrit), masura meaning spots; and from "maselen" (Fourteenth Century English), etc.

What appears to be a fairly intelligible description of both measles and small-pox was first found in the writings of one Ahrun, a native of Alexandria, a physician by occupation (and a priest also, it seems), A. D. 610 to 641. The first approximately adequate description of measles is accredited to Rhazes, A. D. 900, and about equal credit is given to Avicenna, A. D. 980 to 1037. Rhazes called the disease "hhasbah" and indicated its separation from smallpox. Withering definitely distinguished measles from small-pox in 1792. Thomas Sydenham (an Englishman) by his brilliant articles drew a distinct line between scarlet fever and measles in 1655.

The term "rubeola" (meaning red) is from the Arabic and was supposed to have been applied first by Haly Abbas in the latter part of the tenth century. This appellation was in turn replaced by the term "morbilli" (Italian), meaning little disease (as compared to small-pox with which it was at that time so frequently confused). The term "morbilli" remained in use until well along in the Eighteenth Century, when Sauvages suggested a return to the use of the term "rubeola," which suggestion was adopted by Cullen and Willan. The term "rubeola" is now the recognized and accredited name for this disease among all English-speaking races.

CHAPTER XIV

RUBELLA

(*German Measles—Roetheln*)

BY WILLIAM A. JENKINS, A.M., M.D.

Definition, p. 301—Etiology, p. 301—Symptomatology, p. 301—Incubation, p. 301—Invasional or prodromal stage, p. 302—Eruption, p. 303—Desquamation, p. 305—Diagnosis, p. 305—Differential diagnosis, p. 306—Complications and sequelæ, p. 306—Treatment, p. 307—Prophylaxis, p. 307—Curative treatment, p. 308—Prognosis, p. 308—Pathology, p. 309—History, p. 309.

Definition.—Rubella may be defined as an acute, specific infectious disease of unknown origin, characterized by a rather long incubative period, short or absent prodromes, mild faucial catarrh, enlargement of the cervical glands and a polymorphous eruption.

Etiology.—Just as in the case of rubeola, so in this disease we may say that climate, season, altitude, soil, sex, race and heredity seem to exert little if any influence. Exposure to cold lowers resistance and thus acts as a predisposing factor. The same may be said of overcrowding, filth, lack of light and poor hygienic surroundings generally. Rubella is essentially a disease of childhood; it is uncommon during the nursing period; fully 75 per cent. of the cases occur under 15 years of age. The disease is rare after puberty, and almost unknown after forty. (One or two cases reported in the literature at 70 years.) Clinically speaking, one attack of this disease is supposed to confer immunity. As a rule, we look upon the report of second attacks as mistakes in diagnosis. (Second attacks are possible, but their occurrence must certainly be very rare.) The organism producing this disease has never been isolated. The chief mode of conveyance is by direct contact. Individuals coming in contact with the disease may act as carriers, even when they do not contract the disease themselves. Towels, clothes, handkerchiefs, bed-clothing, etc., coming in contact with and having been soiled by the patient are capable of carrying the disease. The chief clinical method of conveyance of this disease is undoubtedly the secretions from the mouth, nose and throat.

Symptomatology.—We shall consider the symptoms under the following heads: (1) Incubation; (2) Invasion; (3) Eruption; (4) Desquamation.

(1) **INCUBATION.**—When we attempt to fix a definite and scientific time-limit for the incubative interval of this disease, our difficulties are many and serious. In the first place, it is highly probable that the pre-

incubative interval may be rather long in this disease, i. e., the specific organisms may gain entrance into the system but may remain localized, say in the mucosa of the bronchial tubes, before they invade the general system via the systemic circulation. They have not as yet reached their especial selective tissue. The true incubation has not begun. Secondly, the prodromal period of this disease is notoriously untrustworthy. It eludes all of our attempts to classify it definitely. Occasionally, though infrequently, it may last three or four days. More commonly it lasts only a few hours. In many instances it is apparently absent altogether. This difficulty is a real one and helps to make our calculations untrustworthy. Again it may be that the life-cycle of the causative organism is unusually long as compared to the life-cycle of some of the other infectious agents belonging to this group. To illustrate, the life-cycle of the scarlet fever organism (reasoning from clinical grounds) must be quite short, while in the case of the disease under discussion the life-cycle may be long. We frequently have opportunity (especially in epidemics) to note that a healthy child was definitely and positively exposed to this disease at a certain time, and we may note the appearance of the first symptoms. This is about as close as we can get to the problem. Even this procedure does not take into account the possible error due to the variability of prodromes. A series of successful artificial inoculations, carried out according to rigid scientific requirements, would help us to some extent in our difficulty, but we have no such data. By common agreement the time-limit of the incubative interval of rubella is placed at from two to three weeks.

(2) INVASIONAL OR PRODROMAL STAGE.—There is no such thing as a definite characteristic group of symptoms pertaining to this period. As a general rule the symptoms are mild in character and of short duration—12 to 48 hours—rarely 48 hours or longer; e.g., the child does not feel well, a slight headache is complained of, and if the temperature is taken at this point we usually find a slight rise present (99° or 100° F. [37.2° or 37.8° C.]). There is a fairly constant and definite enlargement of the lymphatic glands about the neck, the posterior auricular, anterior cervical, the submaxillary or all of these groups may be involved. Occasionally a sore throat presents itself, or it may be a mild conjunctivitis; again hoarseness with a brassy cough (mild bronchitis) may present as a prodromal symptom.

A strong, healthy, robust child may not complain at all. The symptoms are overlooked. Hence, some authors speak of cases without prodromal symptoms, the rash being in such cases the first symptom to present itself. The writer, in his experience with epidemics of rubella occurring among children in an institution, has taken occasion to watch and tabulate, with the assistance of a trained nurse, the symptoms of the prodromal period. The method pursued was as follows: After the appearance of a case of this disease, all of the exposed children (eating at the same table and playing and sleeping in the same dormitory) were inspected, interrogated, their throats examined and temperatures taken daily up to the time of the appearance of the eruption; with this method

symptoms were unearthed that under ordinary circumstances would have passed unnoticed. The commonest symptoms noted in mild cases were headache, slight malaise, enlarged glands, and some temperature. It was astonishing how frequently we found (12 to 24 hours before eruption) a temperature of 99° or 99°_+ F. (37.2° or 37.2°_+ C.), practically never over 100° F. (37.8° C.). The prodromal period may be prolonged, e.g., cough and hoarseness with bronchitis and a temperature of from 100° to 103° F. (37.8° to 39.4° C.) may be present for two or three days before the eruption comes out. Very rarely we encounter an instance in which general or systemic symptoms are pronounced and severe in the prodromal stage. There is always some redness and congestion about the mucosa of the upper air passages, with a tendency to the appearance of some irregular slightly elevated reddish spots (the enanthem). This latter, however, is in no wise characteristic. Finally, it is to be remembered that any symptom of rubeola (measles) in the prodromal stage may be duplicated by rubella in the same stage. Fortunately, however, in rubella the given symptom is much milder and there is no definite and characteristic group of symptoms.

(3) ERUPTION.—The eruption of this disease usually appears promptly after 24 hours (or rarely 48 hours) of mild prodromal symptoms. Many authors speak of it as the first symptom to appear. More properly speaking it is often the first symptom to attract attention. Whenever we have a definite eruption it is practically certain that some mild prodromal symptoms were present, although they may have been overlooked or disregarded. The mild erythematous reddening or suffusion of the face which is so common in measles a few hours before the appearance of the eruption, never appears in rubella. The eruption comes out promptly, showing first about the face, then the trunk, next the arms and legs, the order of the appearance of the eruption being practically the same as it is in measles. The eruption passes from the macular to the maculo-papular (sometimes entirely papular) stage, the individual spots are from a pinhead to a split pea in size, usually smaller than the spots of measles. As a rule, the spots are more discrete; there is not much tendency to confluence. The color is usually not so bright a red—more of a faded rose. The eruption covers the body quickly, usually in 24 hours, rarely over 48 hours. Likewise the spots fade rapidly, beginning about the face first, thence on down the body, following the order of the appearance of the rash. Oftentimes the spots are fading on the face when they are at their height on the legs. The duration period of the rash is in the average case three days. (Often a shorter period, rarely a longer one.)

The above is a fairly accurate picture of the average rubella eruption. Let us now turn our attention to some of the *anomalies* or *irregularities* of the rash of this disease. The eruption is sometimes fugitive in character or even absent: only a few spots may show on the chest or back, quickly fading. Cases reported in which there was no definite eruption discoverable are certainly well authenticated. It is not uncommon in

epidemics where a number of children are taken sick at about the same time, most of them showing the usual eruption. To note a case with malaise, enlarged glands, slight fever and some catarrhal symptoms without eruption, under the circumstances mentioned above, there can be no reasonable doubt as to the diagnosis; however, another possible way of accounting for this rare condition presents itself—as the eruption is fugitive in character, lasting only a few hours, the physician did not get an opportunity to see it. If the case should occur in the physician's own family, where opportunity would be afforded to examine the naked body of the child daily throughout the illness, it is more than likely that some spots would have been detected at some time. The eruption may bloom out all at once, occurring on all parts of the body simultaneously. Occasionally the eruption may show only on one area or part of the body, e. g., the chest. The rash in this disease shows no special tendency to become congregated into clumps or blotches. Relapses or recurrences in which a second or even a third crop of eruption comes up are occasionally encountered, the interval being usually from a few days to two weeks.

We noted in the definition of rubella that the disease was characterized by a polymorphous eruption. Accordingly some authors mention the morbilliform type (the type which resembles measles). This is the common type, and it must be admitted that rubella does seem to bear some close relationship to measles. Many of the older writers were of the opinion that rubella was a sort of hybrid form of measles.

Next we read of the scarlatiniform type, where the eruption very closely resembles scarlet fever, rendering diagnosis difficult in some instances. We note in the literature of the subject reference made to observers who thought that rubella might be a mixture of measles and scarlet fever (so-called mixed type), with mention of particular cases in which the eruption resembled measles on one part of the body and scarlet fever on another. Regarding this phase of the subject, we may safely make the following generalizations: First, that in the greater percentage of all cases, the eruption resembles very closely that of measles; second, that the cases in which the eruption resembles that of scarlet fever (to the degree that diagnosis becomes difficult) are to be considered as relatively rare, although we must admit that we do see fairly frequently cases in which the spots are wholly macular, of a faded or wild rose color (not the fiery red of scarlet fever), varying in size from a pinhead to that of an adult's finger-nail.

The progress of other symptoms during the eruptive stage are as follows:

Fever.—It is quite characteristic in the eruptive stage to have some temperature, although often slight (rarely over 100° F. [37.8° C.], but occasionally reaching 102° or 103° F. [38.9° or 39.4° C.]), and of short duration. This fever has no characteristic curve and no peaks or high points. The temperature usually shows in the prodromal stage and tends to rise slightly until the eruption reaches its acme, then quickly declines coincidently with the eruption. The above is the

usual course. If we have complications, or if the individual resistance is poor, or the infection severe and the disease prolonged, the fever behaves accordingly.

Catarrhal Symptoms.—Catarrhal symptoms, if present in the invasional period, persist throughout the eruptive period or even longer; or they may first present themselves with the eruption and remain after it has faded. A coryza of the nasal passages, redness and soreness of the throat, laryngitis, slight hoarseness and mild bronchitis constitute the symptoms commonly seen under this heading. The eye ordinarily escapes. It may be slightly reddened; some epidemics are reported in which a rather severe conjunctivitis was a prominent symptom. Therefore, concerning the catarrhal symptoms, we may say that it is possible to have in this disease any catarrhal symptom that is found in measles; likewise its grade of severity may be the same. Rarely do we have a group of symptoms. It may be the eye, the nose, the pharynx or the bronchial tubes, any one of these singly. Frequently catarrhal symptoms are slight or absent, and they are never sufficiently dependable to be of diagnostic value in this disease.

Glandular Enlargement.—Enlargement of the posterior auricular, anterior cervical or submaxillary glands, any one or all of these groups may participate in the process. Some enlargement is present in from 50 to 75 per cent. of all cases of rubella. (Some observers say 90 per cent.) This symptom shows during the invasional stage and lasts throughout convalescence, sometimes even longer. These glands generally undergo resolution, rarely do they suppurate. When suppuration does take place it is the result of mixed infection. In a few instances, in severe cases, the glands of the axilla and groin have participated in the enlargement. Enlargement of the cervical glands is sufficiently characteristic of this disease to be considered a symptom of diagnostic importance.

(4) *DESQUAMATION.*—As the eruption fades, usually the accompanying symptoms likewise disappear, and these events bring us to the threshold of the period of desquamation. It is unusually short and uneventful. In the average case the skin shows a type of discoloration, often having the appearance of a brownish stain (the remains of the eruption). This stage lasts two or three days in very mild cases and a week or ten days in severer cases. The phenomena of this period will, of course, vary with the severity of the disease and particularly with the amount and type of the eruption. A marked eruption will show considerable discoloration of the skin and most commonly a fairly perceptible branny or scaly desquamation. With a milder character of eruption, the desquamation is less marked or imperceptible. The enlargement of the cervical glands remains throughout this period and sometimes considerably longer.

Diagnosis.—The diagnosis in the average or type-case of rubella is to be made in the main by consideration of the following points: (1) the absence or mild character and short duration of the prodromal stage; (2) the characteristic enlargement of the cervical lymphatics;

(3) the eruption—its rapid appearance, its polymorphous character and its rapid subsidence; (4) the extremely mild character and short duration of the whole process, and its comparative freedom from complications and sequelæ. The laboratory does not furnish us with any data of importance in making the diagnosis in this disease. Diagnosis in sporadic cases is sometimes entirely impossible. For the differential diagnosis between rubeola, rubella and scarlet fever, *see* the accompanying table.

DIFFERENTIAL DIAGNOSIS OF RUBEOLA, RUBELLA AND SCARLET FEVER

	RUBEOLA	RUBELLA	SCARLET FEVER
PERIOD OF INCUBATION.	10 to 14 days.	14 to 21 days.	2 to 5 days.
PRODROMAL SYMPTOMS.	Coryza of upper air-passages (marked). Cough, conjunctivitis, moderate fever.	Often absent (?) mild catarrh, sore throat, cervical glands enlarged almost constantly.	Short duration; headache, high temperature, sore throat, rapid pulse.
TIME OF APPEARANCE OF ERUPTION.	4th day (rarely later) on the face and neck.	2nd day. Face or upper part of trunk.	24 to 48 hours; neck and chest.
APPEARANCE AND DEVELOPMENT OF ERUPTION.	Macule then papule size, split pea to that of a bean. Color—red, changing to a dusky or violet shade; spots show in groups or clusters. The eruption shows over entire body (usually). Duration 4 to 5 days.	Eruption polymorphous. Common type; resemble measles; spots are not so red nor so large, evenly distributed—no groups nor clusters. 2nd type macular, faded rose color; size, pin-head to finger-nail. Eruption disappears in 2 to 4 days.	Punctate, intensely red or fiery red. Slightly rough to the touch. Confluent, appears continuous (a reading glass will show tiny points of white skin all through the eruption). Region of mouth and nose free of eruption.
ERUPTION OF MUCOUS MEMBRANES.	Well-marked and characteristic, especially "Koplik's spots." Small pin-head-sized, reddish spots capped by minute bluish-white points, shown best on cheek opposite molar teeth. Present 24 to 48 hours before skin rash.	Slight maculo-papular- enanthem, about same time as skin-rash (or slightly before, neither characteristic nor diagnostic).	Sore throat, tonsils enlarged. "Strawberry tongue."
CONSTITUTIONAL SYMPTOMS.	Proportionate to severity of eruption.	In average cases, very little if any.	Usually severe; all symptoms increase with the eruption.
FEVER.	Fever-curve has two peaks or high points, one about the middle of the invasional period; the other at the full bloom of the rash.	Very slight as a rule, beginning a few hours before the rash; reaches its highest point as rash comes out.	Usually high; appears even before the rash, rises with the rash and constitutional symptoms and usually disappears with them.
DESQUAMATION.	Branny scales, the rule being 5 to 7 days.	Usually hardly perceptible; may show as fine scales. 3 to 5 days.	Begins in 6 to 10 days. A characteristic symptom. Occurs as flakes or strips, sometimes even casts. There may be 2 or 3 crops of it.
COMPLICATIONS AND SEQUELÆ.	Air-passages, ear, eye, kidneys.	In the average case, none.	Nephritis; ear, throat.
INOCULABILITY.	Secretions from the nose, mouth and throat. The blood.	Secretions from the nose, mouth and throat. The blood.	Secretions from the nose, mouth and throat. The blood.

Complications and Sequelæ.—In this disease complications and sequelæ occur infrequently. It is the rule for cases to recover promptly

without further difficulty. Speaking, then, from a broad clinical standpoint, we have only a very small percentage of complications and sequelæ. A debilitated condition, a severe epidemic, exposure or lack of attention during the attack, all favor the development of complications and sequelæ. The following are some of the conditions occasionally encountered: (*a*) in the mouth and throat: stomatitis, tonsillitis, pharyngitis, catarrh of the eustachian tubes with ear-ache and possibly otitis media; (*b*) in the air-passages: laryngitis, bronchitis and pneumonia; (*c*) in the nervous system in malignant cases we occasionally have high fever, rapid prostration and convulsions or delirium; (*d*) in the urinary system: attacks of true nephritis are occasionally encountered as sequelæ of this disease.

Treatment.—**PROPHYLAXIS.**—Our experience in epidemics teaches us that this disease is readily transmissible. We have every reason to believe that the causative agent is a filterable virus. We are quite sure that the disease is transmitted chiefly by the secretions of the nose, mouth and throat of a diseased individual. The microorganism is certainly in the blood. It is a fairly sure conclusion, however, that it is chiefly the secretions of the nose, mouth and throat that we have to watch in particular. The mode of transmission is most commonly direct from person to person. We know, however, that it is transmitted indirectly through articles, clothing or fomites recently soiled with the secretions and discharges mentioned above. It is probable that the organisms do not live longer than about 10 days on the soiled articles or fomites. Some authors claim that the organisms may live as long as from 20 to 30 days on soiled articles, as, for example, bedding.

The disease is communicable from the very earliest catarrhal symptoms (or even before that), until all traces of secretions have disappeared from the nose and throat.

With the above as a summation of our actual knowledge regarding the causative agent, its method of transmission and its period of communicability, we may formulate methods of control which will apply to the individual himself and likewise to the community of which he is a member.

The methods commonly used to prevent the spread of acute infectious disease are, in general, about the same everywhere. We can do no better than accept the rules laid down for the control of communicable diseases in the report of the American Public Health Association Committee on Standard Regulations Appointed in October, 1916. They are as follows:

“METHODS OF CONTROL

“(A) *The infected individual and his environment:*

- “1. Recognition of the disease: Clinical symptoms.
- “2. Isolation: Separation of the patient from non-immune children and exclusion of the patient from school and public places for the period of presumed infectivity.
- “3. Immunization: None.

"4. Quarantine: None except exclusion of non-immune children from school and public gatherings, from the eleventh to the twenty-second day from date of exposure to a recognized case.

"5. Concurrent disinfection: Discharges from the nose and throat of the patient and articles soiled by discharges.

"6. Terminal disinfection: Airing the clothing.

"(B) *General measures*: None."

CURATIVE TREATMENT.—Generally speaking, this is a very simple matter; little if any treatment is required in the majority of cases. as the child is not sick enough to go to bed. In the average case, a child should be confined to the house, the bowels should be opened with broken doses of **calomel** followed by a **saline**. The **diet** should be modified according to the severity of the case. **Water** should be taken freely at all times, and the body should be kept clean by a daily **bath**. Protect the skin by anointing daily with **carbolyzed vaselin** (**carbolic acid** drops 5 to **vaselin** 1 oz.) or **oil of eucalyptus** and **olive oil**, equal parts of each. During the three or four days of active symptoms in this disease, many clinicians are in the habit of using (especially in young children) **sulphate of quinin** disguised in chocolate syrup (strength grains ii or iii of quinin (0.13 to 0.2 grams) to a teaspoonful of syrup). Dosage is a teaspoonful every four hours. If the urine is scanty and red and there is pain in passage, the following prescription will be found beneficial:

R	
Sp. ætheris nitrosi	f 3 ii (8 c.c.)
Potassii acetatis	3 ii (8 grams)
Lik. ammonii acetatis }	f 3 iss (45 c.c.)
Aq. camphoræ	

M. Ft. Sol. Sig.: Teaspoonful in water every four hours.

(Suitable for a child 4 to 8-years of age.)

For the treatment of special symptoms see similar heading under measles.

Prognosis.—The prognosis in this disease is, generally speaking, good. It is the simplest, and, from the standpoint of clinical manifestations, the mildest of the acute exanthematous diseases. Deaths in uncomplicated cases occur with extreme rarity. The simple character, mild symptoms and the short duration of the average case of rubella constitute one of its danger points. The child is not sick enough to go to bed; the eruption is fugitive, lasting only a day or so; the family in many instances do not call a physician to see the case, they make a diagnosis from other cases in the neighborhood. Such cases are not properly cared for; they are not put to bed, often not even confined to the house. They, perhaps, are allowed to play out of doors constantly and are exposed, get chilled, etc., and in about two weeks the family doctor is called. He finds that the child has an acute endocarditis, or

otitis media or an acute parenchymatous nephritis. When the disease occurs in an epidemic form among poor and ignorant people who live amid unhygienic and unsanitary surroundings the prognosis increases in gravity and the mortality is correspondingly higher. The presence of severe complications and sequelæ increases the gravity of the prognosis. Some epidemics have been reported with a death rate of from 2 to 4 per cent.

Pathology.—This disease has no characteristic pathology. The eruption was fully described above, likewise the characteristic catarrhal processes which are prone to occur in the mucous membranes of the respiratory and gastro-intestinal tracts are analogous to those which occur in the same anatomical situation in rubeola, though as a rule they are much milder. They have received attention under the proper headings. The pathologic changes found present in complications and sequelæ do not *per se* belong to this disease. They are discussed elsewhere.

History.—The history of this disease is shrouded in confusion on every hand. There is hardly any disease concerning which the opinions of competent and careful clinicians show such a great degree of variance. Many have denied the very existence of this disease; others regard it as a form of attenuated measles, still others as an hybrid of measles and scarlet fever.

The epoch-making work of certain observers has given us a clean-cut, universally accepted clinical picture of measles and scarlet fever. No such results, however, have been attained in the case of rubella. Every symptom of the disease is subject to great variation. The rash, the strongest and most prominent symptom of the disease, is no exception to the above rule. In fact, the multiform character of the rash has always proven to be a universal stumbling-block. Certainly the type resembling measles (rubeola-form or morbilli-form type) is by all odds the commonest. The macular type (the spots varying in size from a pinhead to that of an adult finger-nail, and exhibiting a faded or old-rose color) may some day be distinguished as a separate disease. Dr. Clement Dukes, an English physician, in July, 1900, described what he called "the fourth disease." His views are noted by almost every writer, but accepted as proven by none. Bergen, a German physician, in 1752, was undoubtedly one of the first men to present the claims of this disease as a distinct entity. Sufficient grounds for establishing this as a fact is commonly accredited to Maton, an English physician, who, in 1815, pointed out the pertinent facts—that one attack of this disease furnished immunity; it did not, however, protect the individual from either scarlet fever or measles and, conversely, having had scarlet fever or measles or both, did not protect against this disease. Rubella occurs in epidemics, and, as is often the case under such circumstances, presents fairly constant characteristics. The name rubella (diminutive for rubeola) was first proposed by Veala in 1866. The Germans still give to this disease the name of rubeola. Among English-speaking peoples the correct scientific term for the disease under discussion is rubella.

CHAPTER XV

PAROTITIS EPIDEMICA

(*Mumps*)

BY WILLIAM A. JENKINS, A.M., M.D.

Definition, p. 311—Etiology, p. 311—Symptomatology, p. 312—Period of incubation, p. 312—Invasion, p. 313—Progress, p. 314—Anomalies or irregular types of mumps, p. 314—Consideration of special symptoms, p. 315—Laboratory findings, p. 317—Diagnosis, p. 317—Differential diagnosis, p. 318—Complications, p. 318—Sequelæ, p. 321—Treatment, p. 322—Prophylaxis, p. 322—Curative treatment, p. 323—Convalescence, p. 326—Prognosis, p. 326—Pathology, p. 326—History, p. 327.

Definition.—Parotitis epidemica is an acute specific infectious disease of unknown origin, characterized clinically by an involvement of the salivary glands, chiefly the parotid, and a tendency to invade glandular structures elsewhere in the body, especially the glands of the genital tract, notably the testes in the male.

Etiology.—(1) PREDISPOSING CAUSES.—Cold, climate, season, altitude, soil and race seem to exert no influence whatever as predisposing factors.

Sex.—As a rule, most authors say that mumps is more frequent among males; we must remember, however, that most of our statistics are taken from male schools or from army barracks and camps. If we take a view of the disease in its entirety and consider epidemics everywhere, it is doubtful if we can substantiate this assertion.

Age.—Cases have been reported in which a child was born with mumps in an active stage, as, e.g., a case, where the mother developed mumps at the eighth month of pregnancy and her child, born at full term, had enlargement of the parotids and difficulty in swallowing. Instances of this sort are, of course, rare. The disease in this instance had been transmitted through the placental circulation. Mumps may be said to be rare under four years. The period from four to fifteen years is the most favorable time for this disease to appear. This is especially true in civil practice. Cases in young adults are fairly common in the epidemic form in schools and army camps, but relatively uncommon in civil life.

Mumps rarely attacks an individual past middle life; however, cases are occasionally reported. Heredity or family predisposition is never a factor. Fatigue, hardships and exposure, coupled with overcrowding and poor hygienic surroundings, generally all act by lowering resistance, and thus secondarily they become predisposing factors. One

attack usually confers immunity, but cases are reported in which there were second or even third attacks. Relapses are uncommon, but do occasionally occur, as the literature of the subject will verify.

(2) **EXCITING CAUSES.**—We have every reason for placing this disease in the class of acute infectious diseases, for it is contagious or transmissible, it occurs in epidemics, it has an incubative interval, it has a definite clinical course, it is accompanied by fever and has possibly a blood-picture, a lymphocytosis, which is perhaps both relative and absolute.

The specific microörganism of this disease has never been isolated. Many workers have discovered organisms from the secretions of the mouth and from the blood or from punctures of the parotid glands, and have made the claim that the organism discovered by them was the specific organism of the disease. These reports are all lacking in confirmation. Numerous instances are to be found in the literature of the subject where the secretions of the mouth, taken from a subject suffering from mumps, were filtered and the filtrate used to inoculate lower animals, for example, the cat, with the result that an inflammatory process occurred in the parotids, followed even by atrophy of the testicle. Work of this character may serve to verify the transmissibility or contagiousness of this disease, but has not thus far thrown any light on the specific organism. The organism is certainly in the blood, but is most commonly supposed to abound in the secretions of the mouth, throat and likely the nose. The chief method of conveyance of this disease is certainly by direct contact from patient to patient. An individual who comes in contact with a case and handles articles soiled by the patient may carry the disease to others, without taking it himself.

Finally, it is more than likely that bed-clothing, towels, handkerchiefs, etc., soiled by an individual having mumps may retain organisms for a variable period (ten to twenty days), and thus furnish opportunities for infecting other individuals. The original infection in all probability gains entrance into the system through the nose; then it either becomes admixed with the secretions of the mouth, and travels directly up the ducts of the salivary glands (e.g., Steno's duct to the parotid), or, which is more probable, it is first taken into the general circulation and is later by this means carried to the salivary glands as the tissue of special predilection.

Symptomatology.—**PERIOD OF INCUBATION.**—It is commonly conceded that the incubative interval of this disease is quite long as compared to the same interval in the exanthematous diseases, for instance. Some of the factors, brought forward by competent and experienced observers, which may be taken into consideration as throwing some light on the confusing statements regarding the true limits of this period, are as follows:

(1) The possibility of a long pre-incubative interval. The causative organism may gain entrance into the body, but may be held up in a location unfavorable to growth for quite an appreciable period of time.

after which it may be transported to its particular selective tissue, where growth really begins.

(2) The prodromal or invasional period of this disease is definitely known to be exceedingly variable; some authors report well authenticated cases, too numerous to be overlooked, in which definite prodromes were noted for a week before the enlargement of the parotid gland appeared. Other competent observers give it as their opinion that at least twenty-four to forty-eight hours of mild prodromal symptoms is the rule, while still others appear to regard prodromal signs as the exception. These latter observers count the enlargement of the parotid gland as the beginning of symptoms.

(3) The life-cycle of the specific organism of mumps may be an unusually long one; this possible explanation of the long incubation in this disease must certainly be given due consideration, as it meets most of the needs of the problem to a nicety.

(4) It is to be borne in mind that microorganisms, generally speaking, gain in virulence under favorable conditions of growth, and that, conversely, under unfavorable conditions they tend to lose in virulence, or become attenuated. Any of the above factors may play a part in the determination of the time-limits of the incubative interval of mumps. The causative organism has never been isolated; therefore, we cannot make cultural experiments. Artificial inoculations, in the human species, at least, have not been successful: hence we cannot try out or verify any of the above statements. Some clinicians report cases with an incubative interval as short as four days; others say the minimum period is eight days; again, cases believed to be authentic are reported in which the incubative interval was as long as thirty days. A child in the initial stages of mumps—before the diagnosis is made—may be admitted into an orphan asylum or children's hospital, and after the child has mingled freely with the other children his parotid gland may enlarge; he has fever and a diagnosis of mumps is made. We may now observe the exposed children for the first symptoms of mumps. Usually the first case (or cases) develops in approximately fourteen to twenty days; the above method of clinical observation is at the present time the only reliable means at our command from which we may draw conclusions as to the time-limit of this period. From a clinical standpoint, then, we say with a fair degree of certainty that the time-limit of the incubative interval of mumps is from two to three weeks (fourteen to twenty-one days).

INVASION.—In the average case of this disease, we have a fairly characteristic group of invasional symptoms: usually chilly sensations and restlessness for about two days, and very commonly aching pains about the joints and limbs. The throat feels dry and sore; some temperature is noted at this time, usually 99° - 100° F. (37.2° - 37.8° C.) (occasionally running as high as 102° or 103° F. [38.9° or 39.4° C.]); loss of appetite is almost universal, and gastric irritation, nausea and vomiting may be present. After about forty-eight hours of the above symptoms, pain is complained of in one or the other of the parotid

regions; slight swelling is now noticed in the affected parotid gland; deglutition or swallowing becomes difficult; the patient does not like to talk or open the mouth wide. Oftentimes at about this time considerable pain in the ear is complained of. The disease may now be considered to be definitely developed.

PROGRESS.—The affected parotid—either the right or the left; there is no definite predilection for the process to begin in one side or the other—becomes markedly enlarged, usually filling up the space immediately below the ear between the ascending ramus of the inferior maxillary bone and the mastoid process. The gland becomes much enlarged and the subcutaneous structures in the immediate neighborhood become involved. (Occasionally the submaxillary gland enlarges at the same time.) The patient now presents a very characteristic and oftentimes grotesque appearance, this being especially true if both sides are involved at the same time. The facial appearance is so changed that the individual may be unrecognizable. The malaise and slight aching of the joints and limbs remain and often become intensified; the child is hardly able to swallow or even open the jaws; the mouth is usually dry.

The fever continues— 100° – 103° F. (37.8° – 39.4° C.) as a rule; the glandular swelling usually reaches its height in about three or four days, lasting altogether about five to ten days. Very commonly, as the swelling begins to subside, the opposite parotid begins to pain or show some swelling, and in turn passes through the same stages as the gland first involved. The overlying skin often has a tense, glazed appearance and the parotid has a doughy feeling, or it may be very hard. The tissues overlying the involved parotid may be entirely normal in appearance. Clinically speaking, in the average or type case of mumps, the order of the glandular involvement is about as follows: First and most commonly, we have the involvement of first one parotid and then the other. Generally the second gland becomes involved about the time the first one begins to subside. (Sometimes, but more rarely, the inflammatory process in the first gland disappears entirely and there is an interval of quiescence of four or five days before the second gland becomes involved.) Second, both glands may be involved at the same time, giving the patient a grotesque and unrecognizable appearance, as mentioned above. Third, the disease may develop on one side only, when only one parotid gland becomes involved throughout the course of the disease. Very often the whole disease process may be over in four or five days, or it may last for ten days or two weeks. With the disappearance of the enlargement of the parotids, in a typical case, all the other symptoms subside and the patient gets well promptly.

The above description will fit fairly well the average case of mumps. Let us now turn our attention to some of the anomalies or irregularities of this disease.

ANOMALIES OR IRREGULAR TYPES OF MUMPS.—(1) *Mild or Abortive Type*.—The mild or abortive type is one in which not only prodromal but even general or systemic symptoms are either absent or are so mild that they pass unnoticed. The patient is not ill, the enlargement

of the parotid being the only symptom that makes known the presence of the disease. And even this is not marked and passes away quickly (three or four days) without leaving any traces behind. Cases belonging to this type are sometimes so mild that diagnosis would be doubtful or impossible if the cases occurred sporadically. When, however, these cases occur during epidemics the diagnosis is easy.

(2) *Severe Type*.—The severe type is one in which the individual may be prostrated from the start—with temperature high, heart weak and a low typhoid-like state. Some such cases have been reported as occurring in epidemics by Army medical men. They are never very common.

(3) *Systemic Type*.—Next we have the type in which there are marked systemic symptoms and no inflammation of the parotids whatsoever. Some of the other glands of the salivary group may be involved, for example, the submaxillary or the sublingual; or some of the glands of the genital tract also may be involved, namely, the testes in the male. Some of these cases likewise present diagnostic difficulties. When they occur in the midst of an epidemic the diagnosis is easy; when they occur sporadically great care must be exercised in making a diagnosis.

(4) *Relapsing Type*.—The relapsing type is one in which one group or set of glands is involved at a time—e.g., the parotid and submaxillary or the sublingual group, etc.—with an interval between the attacks: general symptoms accompany each attack, and complications may occur with any one of them. In this connection it may be of interest to quote an instance which very beautifully illustrates the above type. The case in question occurred under the observation of a physician by the name of Karth, and is reported by Jules Comby * as follows:

“In a patient under the care of Karth there were no less than five distinct attacks, each one marked by fever and general symptoms. The first attack, which was the gravest of all, affected the salivary glands, the kidneys and the spleen; the second involved the lacrimal glands; the third, limited to the parotids, enabled a diagnosis of mumps to be made; the fourth was marked by a swelling of the submaxillary glands; in the fifth attack the lacrimal glands were alone attacked. Each successive attack in this series was less grave than its predecessor.”

Those of us who see quite a bit of this class of work can bear witness to the fact that relapses do occur in this disease.

(5) *Chronic Type*.—In this form the parotid glands remain chronically enlarged for weeks or even months after the general symptoms subside. Some slight local manifestations or symptoms may, however, accompany the enlarged glands for quite a long time.

CONSIDERATION OF SPECIAL SYMPTOMS.—The prominent or leading symptoms of the disease are subject to such variations that it seems best just at this point to discuss them *seriatim*.

(1) *Characteristic Enlargement of the Salivary Glands*.—The par-

* Jules Comby on “Mumps,” “Twentieth Century Practice of Medicine,” Vol XIII, p. 577.

otid is the chief gland to be enlarged. It is the most important, the most prominent, and likewise the most frequent and dependable symptom of the disease. In mild cases it is the first symptom to be noted. Usually, first one gland is involved, and as it subsides the other gland becomes swollen. Occasionally both sides are involved at once, and still less frequently only one side is involved throughout the disease. The swelling may be very mild, and again in other cases it may be very marked. A special cutaneous edema appears in the neighborhood of the parotids; often the other salivary glands—the submaxillary and the sublingual—may participate. Now and then the submaxillary or the sublingual alone is involved, proved by the fact that the case occurs in an epidemic and may be accompanied by recognizable complications, namely, the involvement of the testes in the male. Although the whole neck may be much enlarged, as a rule we can readily make out the special salivary glands involved by palpation. Most commonly the skin and superficial tissues are loose and move freely over the gland; occasionally the skin is red, tense and shiny and perfectly tight. The pain and discomfort experienced by the patient are in direct proportion to the amount and character of the swelling. In extreme cases the suffering is great; the slightest touch causes pain; it is very difficult to open the mouth or to swallow, and severe earache is sometimes complained of. On attempting to open the mouth, a tetanic contraction of the masticatory muscles is sometimes present. The lymphatic glands about the neck may become enlarged. The involvement of the salivary glands subsides, as a rule, in about one or two weeks; occasionally it may last longer.

Secondary infection of the involved gland with the formation of pus (suppuration) is a remote possibility.

(2) *The Mucous Membrane of the Mouth and the Salivary Secretions.*—(a) *The mucous membrane of the mouth* in the average case is perhaps dry and redder than usual, and that is about all. In other cases the tongue and mucous membranes are much swollen; the gums are swollen, soft and boggy. The region of the orifice of Steno's duct is infiltrated and stands out plainly; the whole of the pharyngeal ring may be engorged and covered by a slimy secretion. Some authors claim that a characteristic enanthem is present in this disease. This view, however, is not accepted by experienced observers. Stomatitis or even tonsillitis may occasionally be present.

(b) Authors differ much in their statements regarding *the state of the salivary secretions*, but it may be stated as a clinically accepted dictum that, in far the greater percentage of cases, the flow of the salivary secretion is much decreased throughout the active period of the disease. The mouth and throat remain sufficiently dry to cause the patient great discomfort. The secretions tend to become normal in quantity as the glandular involvement subsides. Sometimes in convalescence a troublesome hypersecretion is present for a considerable time. Very rarely one encounters a case which is marked by hyper-

secretion during the active stage of the disease, such cases not being common.

(3) *Constitutional Symptoms*.—In a great many cases, oftentimes even in epidemics, constitutional or general symptoms are so mild that they are said to be absent; their very mildness causes them to be overlooked. But some constitutional symptoms are always present, no matter how mild the case. The most constant and dependable constitutional symptom is fever. In every case in which there is sufficient parotid or other glandular involvement to justify the diagnosis, there is some fever present during the most active stage of the disease. This fever has no characteristic or diagnostic curve; it corresponds with and is directly proportionate to the character and type of the infection. In addition to the fever, we have very commonly, malaise, mild gastro-intestinal disturbance, aching and pains in the joints and limbs (very characteristic and oftentimes lasting several days). Tinnitus aurium, earache, marked pharyngitis and epistaxis are factors which may add themselves to our symptom-group in almost any case.

Finally we have quite a respectable percentage of cases in which the systemic symptoms are marked and even grave from the start.

LABORATORY FINDINGS.—Many authors place great stress on the blood findings in mumps. In the majority of cases we have a slight leukocytosis. The value of this point is somewhat negated by the following facts: (a) the leukocytosis is so slight that it is a question whether it constitutes a leukocytosis or not; and (b) the age at which mumps is most common—from four to fifteen years (childhood)—is a period in which the white cell-count runs much higher normally than it does in the adult. The question naturally then arises, Is it a leukocytosis? Secondly, we have a lymphocytosis which is always relative, and in most instances absolute; further, this finding may be said to be present in all cases throughout the active stages of the disease. Relative lymphocytosis, however, is said by competent authors to be present in several of the infectious diseases of childhood: for example, in anemia, pertussis, bronchopneumonia, measles, etc. Blood-findings, therefore, have very little practical value in this disease. Perhaps, if fever is present and it is a question of differentiating an enlarged parotid gland of mumps from some acute inflammatory condition, such as pus in the gland, the blood-count may help somewhat.

A lymphocytosis of the cerebrospinal fluid is found where we have a meningitis due to mumps, as is noted elsewhere.

Diagnosis.—The diagnosis in the average or "type case" of mumps is easy. The typical enlargement of the parotid gland (most commonly unilateral) presents a characteristic appearance on inspection, and the anatomical outlines of the gland are readily made out on palpation. There is dryness of the mouth and difficulty in mastication and deglutition. The duration of the glandular involvement is relatively short; the swelling comes on quickly and as quickly subsides in from seven to ten days. The above picture, with few symptoms either preceding or following the glandular enlargement, is at once both characteristic and

diagnostic. In irregular or atypical cases, the diagnosis is more difficult. This is especially true where the parotid glands are not involved; perhaps submaxillary enlargement alone is present, or, still more rarely, only the sublingual gland is involved. In the case of the submaxillary or the sublingual enlargement, if prodromal and systemic symptoms are present, and possibly even typical complications, we are able to approach the problem with more certainty.

If the above class of cases occur in the midst of an epidemic, our difficulty is very appreciably lessened. Occurring sporadically or in isolated instances, the above types might be impossible of diagnosis at all. In those very rare cases occasionally reported, where we have systemic symptoms and an orchitis (the salivary glands remaining entirely free), diagnosis is impossible without, and exceedingly hazardous with, the presence of an epidemic. We occasionally see, most commonly in epidemics, cases with grave systemic symptoms from the very start, prostration marked, and the typical glandular symptoms absent or delayed. Diagnosis here is, of course, a matter of great difficulty. The type-symptoms may come out more plainly as the disease progresses. Fortunately such cases are rare.

DIFFERENTIAL DIAGNOSIS.—It should always be borne in mind that the parotids and likewise the other salivary glands may be enlarged from causes other than mumps; for example, non-specific parotitis, due to irritation of some type, such as acute iodism. Again these structures are frequently involved secondarily by infectious microorganisms, the specific type of parotitis. Enlargements in the neighborhood of the parotids (which look like mumps) may be present in tonsillitis or diphtheria; likewise periauricular or cervical lymphadenitis may cause some confusion. In making the differential diagnosis, in addition to the local examination, one should always examine the mouth and throat. A careful history of the case should be obtained and a complete physical examination made before conclusions are drawn.

Complications.—**IN THE MALE.**—Involvement of the structures of the genital tract is by far the commonest type of complication in mumps, and of these structures the testes seem to be the point of special localization. *Orchitis* is rare in children. It is quite uncommon for this condition to be found under fifteen years of age. On the other hand, it is quite common in young adults (after the genital organs are fully developed) and in certain instances where young adults are crowded together, with the elements of exposure and physical fatigue, for example, army barracks and camps, the percentage of orchitis runs very high. Some observers give statistics of epidemics among adult males in which the percentage of orchitis ran as high as 25 to 50 per cent., while others place the average at about one case in every fifteen of the disease. The onset of the orchitis is in most instances marked by (1) sharp and sometimes grave symptoms, for example, high sudden rise of temperature, restlessness and delirium, the affected testicle being much enlarged, heavy, red and painful, with pain running along the course of the spermatic cord. (2) Again it may come on insidiously with

slight or no pain, simply an enlargement of the testicle. The whole testicle is enlarged; the parenchyma of the gland shows the greatest involvement, and, generally speaking, the epididymis is involved also, though to a less extent, the process being in most cases an epididymo-orchitis. This complication usually shows itself in from five to eight days after the onset of symptoms, or, in other words, as the primary point of involvement, the parotid, is subsiding. This is so common that most authors speak of the process as a *metastasis*, i.e., the disease seems to be leaving one part to invade another. In other instances there may be a period of a few days after the parotid swelling goes down before the testicle becomes involved. As a rule, the acute inflammation of the testicle subsides in about three to five days, although some swelling and tenderness on manipulation may remain throughout convalescence or even longer. (3) Finally, as was mentioned under Anomalies or Irregular Types of Mumps, the orchitis may show before the parotid swelling has subsided, or even before its involvement, or without any discoverable manifestations in the salivary glands at all. In this last instance the diagnosis can be made only where systemic symptoms were present and the case occurs in the midst of an epidemic. The above irregularities are possible but not probable. (4) Secondary infection and consequent suppuration may occur in the orchitis of mumps, and such a case is occasionally noted in the literature. The seminal vesicles are quite often involved to a varying extent. Marked tenderness may be noted along their course on examination per rectum. At the same time the prostate may be found to be enlarged and tender; urethral irritation may be present. Cases of non-specific urethritis (no gonococci found) have rarely been reported.

COMPLICATIONS IN THE FEMALE.—In the female the *ovaries* may be involved. This complication, however, is not nearly as common as an orchitis in the male. When ovaritis does occur, it is much less intense than the analogous process in the male. The time of appearance and disappearance of this complication bears the same relationship to the inflammatory process in the parotids as the orchitis does in the male. *Inflammation about the labia* is reported as occurring in rare instances. *Mastitis* or enlargement of the mammary glands has been reported by a large number of observers. It is possible for this complication to occur in either sex; it is much more likely, however, to appear in the female. *Thyroid enlargement* is occasionally noted; it usually subsides in from a few days to two weeks. It is most likely due to toxemia. Enlargement of the lymph glands, *cervical lymphadenitis*, appears to be fairly common. It is always secondary and as a rule does not last long; it may be regarded as an expression of systemic toxemia. *Suppurative parotitis* is a complication which is possible but rarely occurs. One observer with several thousand cases to his credit saw suppuration appear but twice.

GENERAL COMPLICATIONS.—*Acute Pancreatitis*.—Epigastric pain, vomiting and tenderness in the region of the pancreas, with diarrhea and fever, is a symptom-group which has caused the diagnosis of pan-

creatitis as a complication to be made many times. That such an event does occasionally occur there can be no reasonable doubt, for the cases seem well authenticated. It is very likely, however, that many of the cases reported were undoubtedly instances of acute gastric irritation, as part and parcel of the symptom-group in an acute infectious disease.

Mouth and Pharynx.—Stomatitis and sore throat are not infrequent.

The Respiratory Tract.—Complications here are not frequent—edema of the glottis, bronchitis and even bronchopneumonia have been occasionally reported.

Arthritis.—Severe, aching pains about the joints, without the clinical evidence of inflammation, which persist for several days are often present, and are erroneously called "rheumatism." They are simply toxic manifestations of the disease. This manifestation, milder in degree and of shorter duration, occurs in the majority of our cases, as stated above under the head of Symptoms.

The Heart.—The heart is rarely involved in this disease; temporary functional disturbances may arise, but they disappear as the disease subsides. Very rarely, severe cases in epidemics may develop pericarditis or endocarditis.

The Kidneys.—Albuminuria, especially in the moderately severe cases, is quite common—according to some authors, 15 to 20 per cent. Hematuria is reported. Acute nephritis occurs occasionally.

The Nervous System.—Functional disturbances of the nervous system often accompany other complications, e.g., restlessness and delirium with orchitis. In the severe form of the disease, marked toxic effects are produced on the nervous system. Mania, sudden and furious, aphasia, monoplegia and hemiplegia or other types of disturbance are occasionally noted under the circumstances mentioned above. Paralysis of various types occasionally occurs, for example, an inferior paraplegia accompanied by paresthesia and formication. Neuritis occurs in single nerve-trunks or related groups of nerves; even multiple neuritis is encountered now and then.

Owing to its passage through the parotid gland, involvement of the facial nerve is not at all uncommon. Disturbance of the optic and auditory mechanism occasionally occurs.

The nervous system is particularly liable to be involved in grave cases, especially where complications are marked and severe; for example, where the complication of orchitis comes on in a stormy manner, with high temperature, we are very likely to have great restlessness, accompanied by active delirium. *Meningitis* is occasionally seen in almost every great epidemic. This is especially true of mumps in barracks or camps. Sudden deafness may appear at any time in the course of the disease; it may be accompanied by noises in the ear (tinnitus), vomiting, vertigo, etc., or it may appear without other symptoms. Sometimes the deafness disappears; again, unfortunately, it is permanent. No adequate explanation is at hand to account for this sudden deafness. In the majority of the instances of involvement of the nervous system (including even the severe forms mentioned above) ultimate

recovery finally takes place; it may take weeks or even months, however, to accomplish this. In a small percentage of cases the damage is permanent and may result in the death of the patient.

Sequelæ.—Any severe single symptom or any complication which persists, or remains after the manifestations of the disease proper have disappeared, should, strictly speaking, constitute or be spoken of as a sequel. From a strict clinical standpoint, however, it would be best to place in this class only those conditions which follow or come on after, or are the end-result of severe symptoms and complications (*sequor*, Latin, meaning “to follow”).

SEQUELÆ OF THE GENITAL TRACT.—*Testicular atrophy* is an important and fairly common sequel of mumps. Orchitis appears towards the end of the period of parotid swelling, attains a maximum point and subsides usually in about three to five days. Pain, edema and inflammation disappear (some enlargement remains for a time, perhaps a few weeks), the patient is declared well, no further observations are made on him and perhaps some months later, when his physician is examining him for life insurance, the testicle is found to have undergone atrophy. Occasionally the patient comes to his doctor voluntarily and says that the testicle in which he had the mumps has “shrunk.” Atrophy is not noticed because it progresses very slowly and there are no active symptoms. The atrophy begins, perhaps, in about two months after primary involvement and may continue for as long as one year. The atrophy varies in degree; the organ may be decreased in size, one-fourth to one-half, or it may be reduced to the size of a large bean, being very hard and insensible to pressure. Rarely the gland softens, and still more rarely it remains permanently hypertrophied. The amount of damage done depends on (*a*) the amount of testicular atrophy and (*b*) whether one or both testicles are involved. In the majority of instances the enlarged gland is rendered impotent and sterile and, if both glands are involved, the affected individual may be incapable of reproducing his kind, though the desire and the ability to perform the sexual act may remain normal, depending upon the degree of atrophy. Where atrophy is double and complete, practically all of the gland-substance being destroyed, at least so far as function is concerned, the so-called internal secretion is absent, and the affected individual may show some of the characteristics of effeminaey, e.g., the eunuch-voice, enlarged mamma, rotundity of figure, etc. This latter fortunately is exceedingly uncommon. Rarely, the atrophied testicle may undergo suppuration. Likewise the *prostate gland* may atrophy, following mumps. If these phases of the subject were looked into more thoroughly and examinations made more frequently, more cases would be reported. (We have no sequelæ, so far as is known, in connection with the glands of the female genital organs analogous to those described above in the male.) Some hypertrophy of the salivary glands, or even the cervical lymphatics, may remain as a sequel of the mumps.

GENERAL SEQUELÆ.—*The Kidneys.*—True nephritis occasionally occurs as a sequel of this disease.

The Heart.—This organ is rarely involved. Endo-, peri- or myocarditis are remote possibilities. Cases are occasionally reported.

The Nervous System.—Certain forms of spinal or peripheral paralyses, such as were mentioned under Complications, may occur as sequelæ. The conditions usually clear up completely in time, although occasionally some weakness and intermittent paresthesias may persist for years or throughout life. As mentioned under Complications, permanent deafness is sometimes noted.

Treatment.—**PROPHYLAXIS.**—Experience in epidemic work teaches us that this disease is a readily transmissible one. We have every reason to believe that the causative agent is a filterable virus. We are quite sure that the disease is transmitted chiefly by the secretions from the mouth, throat and nose of the diseased individual. The organism is certainly in the blood. It is a fairly safe conclusion, however, that it is chiefly the secretions of the mouth, nose and throat that we have to watch particularly. The mode of transmission is most commonly direct from person to person. We know, however, that it is transmitted indirectly through articles, clothing or fomites recently soiled with the secretions and discharges mentioned above. It is probable that the organisms do not live longer than about ten to twenty days on soiled articles or fomites. The disease is communicable from the very earliest symptom (or even before that) until the time when all traces of enlargement of the parotid glands have disappeared and the leading symptoms have all abated.

With the above as a summation of our actual knowledge regarding the causative agent, its method of transmission and its period of communicability, we may formulate methods of control which will apply to the individual himself and likewise to the community in which he is located. The methods commonly used to prevent the spread of acute infectious diseases are, in general, about the same everywhere. We can do no better than accept the rules laid down for the control of communicable diseases as contained in the report of the American Public Health Association Committee on Standard Regulations, printed in October, 1916. They are as follows:

“METHODS OF CONTROL

“(A) *The infected individual and his environment:*

“1. Recognition of the disease: Inflammation of Steno’s duct may be of assistance in recognizing the early stage of the disease. The diagnosis is usually made on swelling of the parotid gland.

“2. Isolation: Separation of the patient from non-immune children and exclusion of the patient from school and public places for the period of presumed infectivity.

“3. Immunization: None.

“4. Quarantine: Limited to exclusion of non-immune children from school and public gatherings for twenty-one days after last exposure to a recognized case.

"5. Concurrent disinfection: All articles soiled with the discharges from the nose and throat of the patient.

"6. Terminal disinfection: None.

"(B) *General Measures*: None."

CURATIVE TREATMENT.—Treatment consists of: *first*, general management, including the treatment applicable to the average case; *second*, treatment of special symptoms, complications and sequelæ.

(1) *General Management and Treatment of the Average Case.*—In a large percentage of the cases occurring in private practice, the disease is so mild that the patient suffers no inconvenience whatever and little or no treatment is required. Even mild cases should be confined to the house for the active period of the disease (say ten days to two weeks) and if fever is present the case should be confined to bed during the active stage of the disease. The bowels should be cleaned out at the start with **calomel** (alone or combined with **rhubarb** and **soda** or **phenolphthalein**) in broken doses or in a single dose, depending on circumstances and the preference of the attending physician. A few hours after the calomel, **castor oil** or **salines** should be given. The bowels should be kept well open throughout the acute phase of the disease. The **diet** should consist of articles that are easily handled or digested, which should be in the form of liquids or semi-solids, as on account of the swelling and pain it is usually difficult for the patient to open the mouth or swallow. The body should be kept clean by a daily cleansing bath—an ordinary **tub-bath** when not confined to bed, and a **sponge-bath** if so confined. The nose, mouth and throat should be carefully looked after throughout the attack; the mouth should be washed out carefully with plain water after each feeding. About every four hours the nose and throat should be sprayed out with some suitable antiseptic, e.g., **boric acid** 5 per cent., **carbolic acid** 1 per cent., or **chlorazene** 1-1000 to 1-500. (The above measure serves the double purpose of acting as a check on the spread of the disease, and keeping down complications such as stomatitis, tonsillitis, etc., in the individual case.)

Fever.—In the acute phase of the average case, barring complications, fever is not likely to be sufficiently high to demand special treatment; when it is high at this stage, **brisk purgation** and **hydrotherapy** meet the needs of the case as a rule. Occasionally, when the glandular swelling is at its height, the throat quite dry and sore, the patient restless and uncomfortable, with a moderately high fever of 103° or 104° F. (39.4° or 40° C.), a dose or two of the following will be found useful as an emergency remedy:

R

Acetphenetidinigrains iii (0.20 gram)

Caffeinæ citratisgrains ss (0.03 gram)

M. Ft. Caps. No. 1, Sig.: One such capsule every three hours.

(For children from 4 to 12 years of age.)

Usually after about the second dose the temperature drops, restlessness disappears, the patient feels more comfortable and may go off to sleep. Aching pains about the joints and limbs are quite frequently complained of; they may occur at any time throughout the active period of the disease, or even as the symptoms begin to decline. This symptom is often quite troublesome, and it seems to respond quite well to the salicylate group of drugs, e.g.:

℞
Acidi acetyl-salicylici, tablets, grains v (0.325 gram)
Sig.: One every four hours (for a child 10 years or over.)

Or the following may be used:

℞
Sodii salicylatis { āā.....℥ iii (12.0 grams)
Sodii bicarbonatis }
Aq. gaultheriæf ℥ iii (90.0 c.c.)
M. Ft. Sol. Sig.: One teaspoonful in cold water every four hours.

Local Treatment of the Inflamed Glands.—In many instances no treatment is necessary. If, however, much pain is complained of locally, some form of treatment may be instituted. Several layers of absorbent cotton may be placed over the inflamed gland and retained in place by a bandage or cloth bound over the head. Hot compresses, or even a hot-water bottle or electric pad, are occasionally used. In some instances the opposite extreme, cold applications, seem best, such as the use of ice-water cloths, cold packs or the ice bag.

The Use of Drugs as a Local Treatment.—As a local application for use on the inflamed gland, the following prescription may be found useful:

℞
Ung. belladonnæ { āā.....f ℥ i (30.0 c.c.)
Ung. hydrargyri }
M. Ft. Ung. Sig.: Apply locally, as directed.

The above ointment is to be spread freely on a piece of cheese-cloth, and placed on the gland. Apply some absorbent cotton over this. The whole is retained in place by a bandage or cloth bound around the head.

(2) *Treatment of Special Symptoms, Complications and Sequelæ.*—The treatment of markedly inflamed and painful enlargements of the parotids is outlined above. The special measures applicable to fever are likewise given above.

Orchitis.—The best method of treatment of this complication is the *prevention* of its occurrence. In any case of mumps occurring in an adult (from about seventeen years and over) where the disease is at

all severe and is complicated by fever, the patient should be put to bed at once and kept there throughout the active phase of the disease. This measure will minimize the likelihood of orchitis very considerably. If this complication has already occurred, or occurs in spite of our best precautionary efforts, more active measures must be promptly instituted. The bowels should be opened thoroughly and kept open as long as this complication is present. The diet must be reduced to liquids, preferably milk. Water should be taken freely. For the fever use **acetphenetidini**, grains iii or v (0.2 or 0.3 gram) every three or four hours for three or four doses. If this remedy (or some of its congeners) is not effective by this time, it should be promptly dropped, and chief reliance should then be placed on **hydrotherapy**. For the active delirium which is prone to occur with the onset of this complication, the best single remedy is **gelsemium**. (Use whenever possible a properly assayed, physiologically tested, time-limited preparation of this drug, in other words, an active preparation.) The dose should be small and frequently repeated up to physiological effect, namely, the quieting of the patient and the disappearance of the delirium. Some authors favor the use of the **bromids** for the delirium, either **sodium or potassium bromid**, dose suitable to the age of the patient, say ten or fifteen grains every four hours (for age seventeen or over).

Local Treatment as Applied to the Inflamed Testicle.—**Guaiacol** is undoubtedly the best single remedy; 10 to 20 per cent. in glycerin is to be applied freely to the inflamed gland. A nest of absorbent cotton is next fitted snugly around the inflamed organ and the whole kept in place by a loose-fitting suspensory bandage or adhesive strips properly applied to obtain rest and relief from dragging on the cord. The above plan usually meets the indications very nicely, and the swelling subsides ordinarily in from three to five days. Occasionally it may last longer.

The *meningeal irritation* or *meningismus*, as it is now popularly called, which is prone to occur in severe cases during the active or febrile stage, is sometimes a sudden and alarming symptom. In addition to thorough purging, **hydrotherapy** and other general measures as indicated. The above condition is combated by the use of **gelsemium** as directed above, or as some authors prefer, by a combination of **bromids** and **chloral hydrate**, for example:

R		
Potassii bromidi	℥ ss	(15 grams)
Chlorali hydrati	℥ iii	(12 grams)
Aq. menthæ piperitæ	f ℥ iii	(90 c.c.)
M. Ft. Sol. Sig.: Teaspoonful every four hours.		

Occasionally it will be necessary to administer **morphin**, grains $\frac{1}{4}$, and **atrophin**, grains $\frac{1}{150}$, hypodermically for one to two doses. This will usually carry the patient safely through the above described complication. Fortunately, this complication does not last, as a rule, over three to five days in an acute form. If we have a true inflammatory

process of the meninges, however, the story is quite different. True mumps meningitis does occasionally (though rarely) occur. The majority of the cases in the literature are reported by military surgeons as occurring among soldiers. The mortality is very high in these cases, and the treatment applicable will be found under the subject of Meningitis. The treatment of the rare complications and sequelæ of this disease does not, strictly speaking, belong to the average textbook picture of this disease; should they arise, however, their treatment would be along the lines indicated by the particular type of complication or sequelæ, and the circumstances attending thereon.

CONVALESCENCE.—This period in the average case is uneventful; occasionally it may be rather prolonged. The patient is pale and seems to be weak, regaining strength slowly. A particular reason for regarding this period as of some importance is the fact that it is a period of possibilities. The patient is naturally susceptible at this time. The illness was slight, therefore the patient did not take proper care of himself, and exposure and over-exertion invite complications. It, therefore, seems well just at this point to sound a note of warning. Physicians in general should at least supervise the patient throughout this period. It seems to the writer that the convalescent period in all infectious diseases does not receive the attention that it merits from the medical profession. Although all active symptoms of disease may have disappeared and the patient may express himself as feeling well, there is still danger and the patient should be under the observation of the physician for reasons that are obvious. In the severe or grave forms, the period of convalescence will be prolonged in proportion and may be more stormy in character.

Prognosis.—The prognosis, generally speaking, is good; the mortality in this disease is exceedingly low. In uncomplicated cases, no deaths are reported. A death occasionally occurs from some serious complication, e.g., meningitis. In spite of the fact that the mortality is low and the disease usually mild, our experience teaches us that an individual ill with mumps is subject to considerable inconvenience, but of far greater importance is the fact that this is a disease of possibilities. Complications and sequelæ are fairly common, especially in epidemics, and complications and sequelæ may impair or cripple the usefulness of the affected individual temporarily or even permanently.

Pathology.—Our definite knowledge of this phase of the subject is meager. As is agreed by most authors (and verified by the statistics), opportunities for postmortem work are rare. The disease is often crippling but seldom fatal. When death does occur, it is usually due to some complication which is so severe that it masks or obliterates the primary changes. So far as we now know, in mumps proper, excluding complications, the pathology is found chiefly in the salivary glands. The microorganism is supposed to enter the salivary ducts from the mouth, though it may come through the blood stream, and make its way to the gland-substance. The gland-ducts and gland-substance

would then most likely be involved first, and the periglandular tissue secondarily. There is, perhaps, swelling and hyperemia of the walls and linings of the ducts, and likewise of the acini of the glands. The swelling is sometimes so great that the ducts of the affected glands are occluded. (In the case of the parotid gland, Steno's duct may be readily felt with the fingers as a firm cord-like structure.) The periglandular tissue is likewise swollen and inflamed, even edematous, and round-celled infiltration most undoubtedly takes place; no true hypertrophy, however, is supposed to occur. In simple cases nature is usually able to bring about a condition of *restitutio ad integrum*.

The above is approximately the full extent of the pathologic changes in the acute or active stage of the disease. As an end-result we may have an hyperplasia of the parotids which may not clear up for months.

The end-result of the testicular involvement is, as a rule, a parenchymatous sclerosis of the testicle combined with atrophic changes. The pathologic changes, accompanying severe complications and sequelæ, are not, strictly speaking, a part of the pathology of mumps, consequently we shall not discuss them here.

History.—Medical historians inform us that the disease, mumps, was known in ancient times. The venerable Hippocrates, born 460 years before Christ, has left us a description of this disease which is unmistakable. After Hippocrates, clinical knowledge of this disease seems to have been swallowed up in oblivion for over two thousand years. We next find traces of it perhaps in the latter half of the seventeenth century and the first quarter of the eighteenth century (A. D. 1650 to 1725). The writings of various medical observers of the period mentioned above convince us beyond the shadow of a doubt that these men did see *bona fide* cases of mumps, and we are just as thoroughly convinced, from these same writings, that the aforesaid observers did not recognize the phenomena as a distinct disease. In truth, the enlarged parotids were confused with such conditions as the adenitis accompanying ulcerative stomatitis, tonsillitis, diphtheria and other conditions which would produce an adenitis or other type of enlargement about the neck. The subject of mumps during the above period was inextricably entangled in a confused mass, with many of the still undifferentiated acute epidemic infectious diseases. Authors are agreed that Hamilton, an observer of the epidemics of Scotland in 1761, did much towards bringing this disease out of its obscurity. This observer likewise noted the appearance of orchitis as a complication, and to Mangor (epidemic of Wiborg, 1773) is usually given the credit of recognizing mumps as an infectious disease. The study of the epidemics which occurred in Italy about this same period did much to clear up the situation, namely, the epidemic at Florence in 1752, observed by Targioni Tozzetti, and one at Bologna in 1753, observed by Laghi, and the epidemic which occurred in Genoa in 1752. We may safely conclude that the identity of mumps as a distinct disease was established, roughly speaking, about the middle of the eighteenth century (1750). It was recognized definitely as an infectious disease, and was known to

occur in epidemic form; likewise its chief clinical characteristics and its more common complications were noted and accurately described. Mumps seems to defy all seasonal and geographical limitations; it is a disease which has occurred in epidemic form in almost every country of the civilized world; it is very prone to become epidemic where large numbers of young men are congregated together, for example, in schools and among troops in barracks and camps. One strange factor in the epidemiology of this disease is the fact that, as a rule, this disease does not spread rapidly and in the broadcast manner that scarlet fever and measles do. We commonly have an invasion in a school or locality, a certain number of cases occur, the disease dies down and that is the end of it. More rarely, however, mumps does extend broadcast and invade the whole of a district. Epidemics of this sort were described by the famous French physician, Laveran. Similar epidemics in Italy, Switzerland and Sweden have been reported.

The disease under consideration has been known by many names. The Latins called it "cynanche parotida"; among the French it is called "les oreillous"; "the branks" was an old Scottish term for the mumps. The word "mumps" comes to us, perhaps, from the Danish term, "Mompen," meaning mumbling (like an old man), to talk in an imperfect fashion. The swelling about the throat and the inability to open the jaws causes the patient to talk in an imperfect or mumbling tone, hence the popular term or its corruption, namely, *mumps*. The proper scientific term for this disease is *parotitis epidemica*.

CHAPTER XVI

SYPHILIS

BY JOHN H. STOKES, M.D.

- The *Spirochaeta pallida*, p. 330—Infectiousness of syphilis, p. 332—The defense mechanism, p. 333—The course of syphilis in man, p. 335—Dermatologic aspects of early syphilis, p. 337—Mucosal and mucocutaneous lesions of early syphilis, p. 339—Constitutional symptomatology of early syphilis, p. 341—The latent phase of syphilis, p. 344.
- Biologic tests for syphilis, p. 345—The dark field examination, p. 345—Blood serologic tests—General principles, p. 347—Clinical interpretation of positive serologic tests, p. 351—Serologic tests in latent and late syphilis, p. 352—The spinal fluid examination, p. 351—Practical considerations in spinal fluid examination, p. 355—The time to do the spinal fluid examination, p. 357—Interpretation of spinal fluid findings, p. 358—The spinal fluid cell count, p. 359—The globulin estimation on the spinal fluid, p. 360—The colloidal test on the spinal fluid, p. 360—Interpretation of the spinal fluid Wassermann test, p. 361—Interpretation of the so-called normal or negative spinal fluid, p. 362—Interpretation of the positive or abnormal spinal fluid, p. 362—The luetin test, p. 364—Biologic tests in infectiousness and cure, p. 364—Blood tests and infectiousness, p. 364—The fixed positive blood test, p. 365.
- The principles of the treatment of syphilis, p. 369—Modes of action and comparison of the effects of the arsphenamines and the heavy metals, p. 373—Action of the heavy metals in syphilis, p. 377—Discussion of the individual arsphenamines and tryparsamide, p. 379—Discussion of the heavy metals, p. 385—Effect of storage, elimination, route, vehicle and salt, p. 386—Fever and other nonspecific methods in the treatment of syphilis, p. 390a—Diathermy, p. 391a.
- Complications and contra-indications of the treatment for syphilis, p. 392—Preparatory treatment, p. 392—Drug complications as such, p. 392a—Prevention of complications in treatment for syphilis, p. 398a.
- Certain collateral considerations in treatment, p. 403—Dietary management, p. 404a—Principles underlying the therapeutic test, p. 405a—Medical prophylaxis of syphilis, p. 406—Systemic prophylaxis with arsphenamine, p. 406a—The problem of "cure," p. 406a—Diagnosis and treatment in special aspects of syphilis, p. 410—Special diagnosis of early syphilis, p. 410—Standard systems of treatment for use in early syphilis, p. 414a—Relapse and recurrence, p. 415a.
- Special diagnosis and treatment of benign late syphilis, p. 417—Late syphilis of the bones and joints, p. 420—Miscellaneous benign late syphilis, p. 423—Gumma of the lymph nodes, p. 423—Late syphilis of the male and female genito-urinary system, p. 423a—Recurrent and late syphilis of the eye and ear, p. 424—Special diagnosis and treatment of late visceral syphilis, p. 425a—Syphilis of the gastro-intestinal tract, p. 425a—Syphilis of the liver and spleen, p. 426a—Special diagnosis and treatment of cardiovascular syphilis, p. 428a.
- Special diagnosis and treatment of neurosyphilis, p. 433a—Treatment of early neurosyphilis, p. 437—Intensified treatment methods, p. 438—Management of general paresis, p. 440a—Management of the tabetic, p. 440a.
- Familial and prenatal syphilis, p. 442—Diagnosis of tardive prenatal syphilis, p. 444—Blood serologic tests, p. 444a—Prevention of prenatal syphilis, p. 445a—Treatment of the pregnant woman, p. 446a—Postpartum observation, p. 447—Treatment of the syphilitic infant, p. 447—Management of tardive heredosyphilis, p. 448.

Syphilis is an infectious disease due to the *Spirochaeta pallida*; of great chronicity; systemic from the outset; capable of involving practically every structure of the body in its course; of simulating a large proportion of the entities comprising the field of medicine and the specialties; transmissible to offspring in man; transmissible to certain

laboratory animals; and specifically treatable to the point of presumptive—but not thus far demonstrable—cure by the use of derivatives of arsenic, mercury, bismuth, the iodides, and fever therapy.

There is no proven absolute insusceptibility to the disease on the part of an uninfected person. Differences of susceptibility have, however, been suspected and supported by case reports. The known influences predisposing to infection are all local in character and concern the biology of the organism. Thus the presence of an absolute or relative anaerobiosis plus moisture due to body secretions greatly increases the likelihood of infection at the point where the organism is deposited. Abrasion of the receiving surface is not necessary to inoculation. Influences of a general character act rather through social than through medical channels. Alcoholism thus contributes to the incidence of syphilis by rendering the individual incautious and indiscriminate in the face of exposure. Lapse of time after contact acts predisposingly by causing delay in the adoption of individual prophylaxis. It is probable that by no means all exposures result in infection, but the complete understanding of all predisposing and all protective influences has not been achieved.

Syphilis, once established and in a state of symptomatic latency, however, is definitely subject to the exciting or reviving effect of trauma, and to the influence of the so-called *locus minoris resistentiae*.¹ Dirt and irritation about the mouth and genitalia predispose to the appearance in these sites of active infectious lesions. Trauma upon a bone in a patient whose more advanced infection is latent may result in the development of a gumma. Trauma and stress or physical injury to the nervous system tend to favor the appearance of active involvement of these structures. It cannot be said, however, that there is a distinctive constitutional habitus associated with a favorable or an unfavorable course of a syphilitic infection. There is a definite type of relapsing patient who with difficulty, if ever, controls his exacerbations of infectious lesions. What makes him such is entirely unknown, though there has been observed the association of such lack of resistance with the mechanism of the Wassermann reaction and with the occurrence and acuteness of the early cutaneous reaction (secondary eruption).² Inter-current disease and syphilis often unfavorably influence each other especially where tuberculosis is concerned. On the other hand, illustrations of lack of effect seem quite as numerous as the reverse; and intercurrent febrile disease may even, through the pyrexia, as in the case of malarial therapy, actually have a beneficial effect.

The Spirochaeta Pallida.—This micro-organism, identified in 1905 by Schaudinn and Hoffmann, has been accepted as the cause of syphilis. It is a spiral organism, very delicate, $0.25\ \mu$ in diameter and averaging $7\ \mu$ in length, with limits of 4 to $24\ \mu$. The turns in the spiral range from 6 to 24, and the average ratio of length of turn to width is 1:1.2. The spiral is peculiarly rigid, keeping its twist and showing like a brilliant, coiled lamp filament in a good dark field. The motility is even more characteristic than the shape—a motion of translation, a slow rotation on the long axis like a corkscrew, and a waving or twisting movement from side to side. The organism is found in abundance in the exudates and tissues of the early lesions of the disease; and is demonstrable by animal inoculation, though found with greater difficulty microscopically in the late syphilitic lesions of all structures, including

the liver, the heart and great vessels, and the nervous system. One or two notable exceptions to this statement, however, have recently led to a more determined search for evidence of a granular or ultramicroscopic stage of the organism, and, by inference, for other evidence of a life cycle. Notable among the exceptions is the extreme difficulty of finding organisms in infectious semen, and in the pulp and fluid of maeerated or ground lymph nodes of rabbits, which none the less are capable of carrying the infection to other animals. Recently, Levaditi and his coworkers,³ and Warthin and Starry,⁴ have discussed this question, bringing forward evidence for the existence at least of a minute granular stage whose place in a possible life cycle, as the latter authors wisely remark, remains to be determined. There can be no doubt that some of the puzzling problems of the prenatal infection of the child with syphilis would be greatly clarified by the demonstration of a very minute or ultramicroscopic form capable of being conveyed within the head of the spermatozoon; and some of the peculiarities of asymptomatic latency would likewise probably be better understood.

The so-called laws of Koch have never been completely satisfied, apparently, with reference to the accepted cause of syphilis, in that no one has yet succeeded in cultivating a virulent *Spirochaeta pallida*, in spite of numerous attempts.^{5,6} All successful culture of the organism has been by way of preliminary rabbit inoculation. It is evident therefore that one of the vital links from which to materialize the chain of events in the life history and immunology of syphilis is still missing. Noguchi himself, as the first cultivator of the organism, has pointed out the extraordinary range of deceptive possibilities in the identification of the organism among genital spirochetes, both microscopically and in culture.⁷

Strains of the *Spirochaeta pallida* are known to exist (Nichols, Truffi, etc.), and have fairly definite biologic characteristics as expressed in their behavior within the animal host. The attempt to make the definition of these characteristics too clear-cut clinically, as in Levaditi and Marié's dermatropic and neurotropic strains,⁸ has not, however, met with unqualified acceptance. None the less, recent experimental work has shown that two strains of organism may be carried at the same time in the same animal and be distinguished from each other by a process of cross-infecting fresh animals from the tissues of the carrier.⁹ These and other extended studies of the immunity mechanism in syphilis by numerous investigators—including Neisser, Finger, Uhlenhuth, Kolle, Schlossberger, Prigge, and others, in Europe; and Brown and Pearce¹⁰ and Chesney¹¹ in this country—make possible the following condensed statement of the course of a syphilitic infection from the standpoint of organism and host relations.

When favoring external conditions permit the entry of the *Spirochaeta pallida* into the body, the succession of events so far as visible reaction is concerned varies with the site and mode of inoculation. As a rule in man a chancre appears, but such a local papular reaction is by no means necessary, to judge from animal experiments. There may be little or no local reaction in the skin and subcutaneous tissues, but a marked reaction at the site, with formation of an eroded or ulcerative indurated papule. Or, there may be no chancre; instead a marked reaction in the adjacent lymph nodes (chancreiform adenopathy). An extremely important fact for the practitioner to grasp, and one long

misunderstood and mistaught, is the rapidity of dissemination of the organism from the point of entry. In striking contrast to the slow development of the chancre or local reaction, the organism disseminates at once, and can be found in the spleen and testis within 24 hours.¹² It is abundant in the blood stream within the week after inoculation, though there are no signs of constitutional reaction except in rare instances. It must be realized that syphilis is therefore, from the moment of its invasion, a general, not a local infection. It must therefore be dealt with as such.

There is a distinct tendency to elective localization of the *Spirochaeta pallida* in both man and animals which is not, however, as yet worked out in detail. The spleen, the bone marrow, the testis and the lymph nodes are especially affected. The last mentioned may be carriers of the disease when no other focus can be identified; and Raiziss¹³ has recently shown that if the *Spirochaeta pallida* is introduced into the cerebral ventricles, the rabbit develops, not neurosyphilis but a testicular chancre. The organism is recoverable from the blood during both the early active and the latent or quiescent stages of the disease, even with a negative Wassermann reaction; from the milk, from the semen, and even from the normal as well as the abnormal spinal fluid.

The vascular localization of the *Spirochaeta pallida*, amounting almost to a tropism, but of course inevitable from the blood stream distribution, is one of the most significant facts of the disease in man. Its realization underlies the comprehension of much of the varied symptomatology. Practically no infected human being escapes vascular involvement. On the other hand, vascular and myocardial syphilis in the rabbit is as yet not proven to exist. Warthin¹⁴ states that the heart of every latent male syphilitic shows vascular lesions, while that of the female rarely does. The negro is notably susceptible to syphilitic vascular disease. Though its vascular phase is important, involvement of the nervous system undoubtedly shows many indications of being in part a tropic phenomenon; but its clear-cut demonstration as such is not yet accomplished. Study of the localization of relapse lesions suggests that there is almost a definite tendency for the organism to favor the genital region as an elective localization in the early states of the disease.

Infectiousness of Syphilis.—Certain characteristics of the *Spirochaeta pallida* as an organism have great practical importance. The resistance and viability of the organism is fortunately low, so that it is easily destroyed by the weakest disinfectants and also by drying. Even a papular cutaneous syphilid is noninfectious so long as the surface of the lesion is intact and dry, and there is no occasion for the disinfection of living quarters and fomites provided they are dry. On the other hand, great stress should be laid on this contrast: the *Spirochaeta pallida* is one of the most ideally constituted of all pathogenic organisms for the invasion of and for undisturbed parasitic existence in man. A little moisture, especially from discharges, protects it and maintains its viability and virulence. Infection takes place too often when least expected, and in spite of what may seem to be all reasonable precaution. Unawareness is, therefore, the great danger in encountering syphilis and increases every type of risk in both physician and patient. The peculiarities of the organism explain the genital transmission of the disease, for only about the flexures and in and near the mucocutaneous orifices are the requisite combinations of moisture, erosion of

lesions liberating spirochetes, and quasi-anaerobic conditions combined. Syphilis is, therefore, inevitably a disease of intimate contacts and, moreover, of intimate contacts rendered unguarded by emotion, by inconspicuousness or concealment of infective lesions, by painlessness, by ignorance. Kissing and sexual intercourse are therefore the overwhelmingly frequent source of acquired infection with syphilis.

The fact that the *Spirochaeta pallida* so closely resembles certain other spirochetes of the mouth and genital tract; that its differentiation thus far depends particularly upon its living characteristics, especially its motility; that this necessitates the cumbersome dark field apparatus for recognition instead of the relatively simple stain; that identification of the organism is a matter for expertness at the stage when no other test thus far devised for identifying the disease gives early enough warning for the highest proportion of "cures" and the need for prompt recognition of infectiousness—all these facts taken together explain the peculiar difficulties of the control of syphilis as an epidemiologic problem. The therapeutic means are at hand. What is lacking is simplified early diagnosis.

The Defense Mechanism.—Following the entry of the organism into the body and its dissemination by the blood stream, innumerable foci of reaction are established in the tissues. From them, through a cellular and not a humoral resistance mechanism, comes the defense which the body makes against the disease. The syphilitic process is immunologically a local one, reduplicated in all individual lesions from the chancre on the penis to the miliary gumma in the aortic wall or the brain substance. The rise, development, decline, and recrudescence or relapse of the local focus, with lymphocytic infiltration and with spirochetal multiplication followed by fragmentation and degeneration, is a universal feature of the process. The immunity mechanism thus set in motion, though its nature is as yet obscure, is responsible for the succession of pathologic lesions and changes observed in the infected individual.

The first type of immunity developed by the infected person is so-called chancre immunity, or resistance to reinoculation. Appearing within the first several weeks, this immunity may be prolonged, or of short duration. It is followed by the still controversial, permanent systemic immunity or resistiveness to reaction. It must be clearly understood that this lasting immunity may not involve the destruction of the organisms present or of those that may subsequently invade the host. In other words, the host may remain a carrier and disseminator without himself showing any tissue or humoral reaction to the organisms in his tissues. Vast numbers of spirochetes can be found in the congenitally syphilitic heart, yet congenital syphilis of the heart is a clinical rarity. The question as to whether this immunity to reaction, prolonged or permanent, can exist without the presence of the organism is a critical one today, and two schools maintain the alternative possibilities. What one might call the Kolle group¹⁵ believes that immunity exists only in the presence of the organism, and that the symptomless individual with syphilis is simply a nonreacting carrier, not a "cured" individual. On the other hand, the Brown-Chesney group has sustained, and apparently proved, the contention that a permanent immunity to syphilis may be developed by the disease and continue to exist after the last organism has disappeared. Around these immunologic contentions center not only the vital question of the cure of syphilis but important possibilities

involving its transmission. It appears that protective reaction to syphilis varies tremendously with the individual and species, with the mode of inoculation already mentioned, with the season, with the diet and living conditions, and perhaps with the strain of organism. Absolutely passive carriers have been found among animals, such as the rat, which, while infected and carrying the organism indefinitely, never react with the production of lesions. Kolle has even gone so far as to suggest that such passive carriage exists in man, in the persons of patients who, without signs of local reaction such as a chancre or secondaries, are found in the later years of life to have developed syphilis and to have infected their families. The nonappearance of lesions is no evidence that an individual has escaped infection or is cured, as professional persons who carelessly invite needle pricks from instruments contaminated with syphilitic blood may have cause to remember. Even the healing of a lesion of syphilis, since it is a local immunity reaction, has no necessary value as a sign of cure.¹⁶

The Question of Cure.—Latency and relapse are then the two fundamental and established facts of a syphilitic infection. Reinfection, superinfection and cure are still within the penumbra of doubt. The range of carrier possibilities thus looms discouragingly large. It is well known from animal experimentation, that an individual harboring one infection in a latent state may acquire another as a superinfection and transmit it without outward evidence of reaction in the form of lesions. The work of Hashimoto,¹⁷ while awaiting confirmation, suggests that superinfection in man actually can occur, and that it cannot be distinguished in course from so-called reinfection. This, too, is known definitely to be the case in animals. Reinfection and superinfection, therefore, tend to become indistinguishable, a viewpoint supportable to some extent even on clinical grounds. To the supreme question for the individual—"Is there cure?" no conclusive answer for man can be given. There is practical certainty that in relatively resistant animals, such as the rabbit, actual and complete cure is possible—at least, an organ hash fails to transmit the disease. But for man, thus far, the only demonstrable status is clinical arrest or asymptomatic latency with nontransmissibility—the "cure" written with quotation marks, as used throughout this presentation. With "cure" in syphilis, hope needs constant and determined differentiation from certainty for perhaps another hundred years.

Hypersusceptibility or "Allergy"—Malignant Syphilis.—The practicing physician, then, in dealing with syphilis must realize that an immunity reaction does develop, and that it is a variable and uncertain, but none the less real, asset in dealing with and interpreting the disease. Certain modifications of the general concept of a developed immunity reaction require special mention for their practical significance. The first of these is the "allergy," the "Umstimmung" of Neisser and his coworkers. An unknown proportion of syphilitic patients develop not alone a resistance to the disease, but an allergic susceptibility to it, by virtue of which a few isolated organisms late in the disease set up a degree of local reaction at a residual focus, which is severe out of all proportion to the amount of virus present. This is one of the factors in the development of gunma, and of all the conspicuously destructive lesions of late syphilis, though it is contended that the vascular changes characteristic of the course of the disease may explain much that was

earlier called allergic response. *The luetin reaction* is an example of allergic response; and its nonspecificity and the ease of imitating it with other adsorbent agents tend to indicate that the allergic mechanism itself in syphilis is not a highly specific affair. Allergy underlies in all probability the course of what is spoken of as *malignant syphilis* or precocious tertiarism, in which the patient, at the onset of his disease, and before his secondary eruption is fairly upon him, begins to develop large and widely disseminated lesions of a highly destructive type. That allergy involves a lack of resistance of the patient, and likewise in all probability a superior resistance of the organism to specific medication, appears from the failure of some of these patients to respond to any treatment whatever.

Treatment of Allergy.—Even more important, because too often a sequel of the practitioner's management or the patient's neglect of treatment, is the fact that the allergic hypersusceptibility may follow upon and be induced by insufficient treatment, especially with the arsphenamines. The effect of a short course of an arsphenamine without ensuing mercury or bismuth is to deprive the patient of the defense which his own tissues would have developed had the organisms been present, and to provide no substitute for it. The resultant relapse when the partially sterilized patient is again flooded with the multiplying organisms, is too often raised to fulminating severity by an added allergic susceptibility.

The Course of Syphilis in Man.—Keeping in mind the fundamental facts thus far reviewed, the clinical course and biology of syphilis in the human subject may now be summarized. The invasion of the tissues by the *Spirochaeta pallida* may or may not, as has been noted, be followed by a recognizable local reaction. If such occurs, the incubation period ranges from 7 days to 30 or more, with an average range of 10 to 21 days. During this period, invasion of any and all tissues of the body may and probably does occur, with localizing predilections for certain sites. Some patients from the very start, for example, show evidence of involvement of the nervous system. The development of the primary reaction or *chancre* always takes place at the site of inoculation or in its immediate lymphatic drainage. While the lesion is usually solitary, chancres may be multiple, as high as 20 having been reported in a single case. Auto-inoculative effects may be observed occasionally. The lesion, if uncomplicated, tends to be relatively painless (chancre of the finger may be a notable exception). There is induration of the base of the lesion in the large proportion of cases, and erosion of the surface is the rule rather than ulceration. The size of the fully developed chancre may vary from that of a pin-head to an area as large as the anterior surface of the scrotum. The border of the more typical lesions tends to be defined sharply and shows a fine hemorrhagic line at the periphery of the erosion which is not ragged, undermined or necrotic unless complications have set in (chancreoid). The base tends to be clean, with a faint grayish pellicle or a raw muscle color. The exudate is serous rather than purulent. The *indolence* of the lesion, which tends to run a slow course of three to eight weeks, is a very important characteristic. Even more important is the development, in about 70 per cent of the cases, beginning from the seventh to the ninth day, and often earlier, of a satellite, painless, noninflammatory, discrete, usually bilateral *enlargement of the lymph nodes* constituting the immediate

lymphatic drainage of the chancre site. The notable exception to the bilateral character of this adenopathy is, of course, the extragenital primary lesion. With or without treatment, the primary lesion undergoes spontaneous involution, the induration of the site and the enlargement of the satellite lymph nodes persisting for several weeks to months and being revivable by trauma, as Klauder and Solomon¹⁸ have shown. The ultimate scar is, contrary to common conception, usually so slight as barely to be detectable.

During the early days of the chancre, the *Spirochaeta pallida* is usually abundant in the discharges from the untreated lesion. The blood Wassermann reaction is negative for a period at the outset, varying with the technic employed, from the seventh to the fourteenth day. The Wassermann reaction and a modification of the Kahn precipitation test (Kolmer and Klauder,¹⁹ and Elliott²⁰) yield positive results on the chancre serum much earlier than the positive obtained from the blood. The immense diagnostic significance of this series of interrelations will be considered later, but can hardly be overemphasized. After the second week of the chancre, the organisms become difficult to find, while the Wassermann and precipitation tests show a rapidly increasing and high proportion of positives.

Primary Syphilis in Women.—There are notable differences between the chancre in the man and the woman, to which special attention should be called. The site of the chancre at the point of inoculation brings the lesion in women all too frequently within the genital tract, where it is unrecognized by the patient and not looked for by the physician. The chancre of the cervix, moreover, is one of the most ephemeral and short-lived lesions of the disease and, if seen, is usually mistaken for an erosion. The chancre in women occurs on the cervix in 44 per cent of cases, according to Davies.²¹ The chancre on the external genitalia of the woman is likewise short-lived and inconspicuous, and often with little or no perceptible induration. All these considerations contribute to make the inability to identify syphilis in the primary stage in women one of the chief factors in the perpetuation of the disease as a public health problem. On the other hand, aberrant cases of cartilaginous induration and hypertrophy of the chancre, both on the cervix and labia and at the urinary meatus, have led to mistaken diagnoses of carcinoma.

Too much emphasis cannot be placed upon the morphologic variability of the chancre. A chancre may look like almost anything, occur almost anywhere on the body except the hair, nails and teeth. The physician whose concept of the onset of syphilis is limited to the mental picture of the typical or "Hunterian" chancre here described will miss many of the primary lesions which present themselves to him for treatment—most of them under the diagnosis of chancroid. The diagnosis of primary syphilis, as will presently appear, is largely a problem for the laboratory.

With the appearance of the chancre, the secondary incubation period of the disease begins. During this time, varying from three weeks to four or even six months, the multiple foci of deposit of organisms from the blood stream begin their local reactions, and the general refractoriness of the patient to reinoculation and the development of an active defense takes place. There is thus no distinct line of demarcation immunologically or even clinically between the primary and the so-called

secondary stage. It is best, therefore, to include the two under the more modern designation of early eruptive or florid syphilis. It is important to realize that as high as 60 per cent of patients found in later life to have syphilis can give no history of lesions suggestive of the secondary stage, though because of their inconspicuousness, they may have been present and been overlooked. It should further be emphasized that the superficial conceptions of syphilis as a skin disease and a surface affair arose from the overemphasis placed on the widespread lesions of the skin and mucosae in secondary syphilis. These, as a matter of fact, are trivial both in appearance and in significance for the future of the patient, though vital to the problem of controlling the spread of the infection. So far as the patient himself is concerned, the really significant events are all going on beneath the surface. Involvement of the heart and aorta takes place, the complication which, under an impenetrable veil of five to ten years of silence with respect to symptoms, prepares the way for what is in all probability the most disastrous aspect of the disease for the patient himself. The invasion of the nervous system, suspected perhaps in occasional cases because of headaches, a nerve palsy or a grouped follicular syphilid with alopecia, is at this stage of syphilis only detectable in the vast majority by the examination of the spinal fluid. It is most essential, therefore, that the attention of the physician be turned, so far as the welfare of the individual patient is concerned, from the material of the textbooks of the past generation—the dermatology of syphilis—to the modern degeneration-preventing measures for recognizing and treating visceral, vascular and neurosyphilis before symptoms of these complications have developed. Once this is done, the cutaneous and mucosal aspects can be studied chiefly for the aid they lend in diagnosing the disease, rather than as the disease itself; and principal attention can be paid to their paramount public health significance as the bearers of the organisms at the surface of the body, and the source of the transmission of the infection.

Dermatologic Aspects of Early Syphilis.—From the conventional illustrations of early cutaneous syphilids, it is easy to derive the impression that they are frequently conspicuous and hence unescapable in the clinical examination of the patient. Exactly the contrary is, however, the case. The pustular, rupial, annular and varioliform syphilids are relatively uncommon, and the large proportion of common eruptive manifestations of the secondary period are fugitive, inconspicuous and easily misinterpreted. Eighty-five per cent of secondary syphilis is seen with difficulty under artificial light or in the illumination of many offices. Good light, uniformly available in the physical examination of all patients, would materially change our impressions of the "florid" stage of syphilis. The same principle applies to the recognition of the mucosal and mucocutaneous lesions. They are missed, first, because of the overlooking of their sites in physical examination, and, secondly, because of inadequate lighting. This is the appropriate point at which to drive home the fact that an examination of the patient which does not include a careful inspection of the tongue, buccal mucosa and pharynx, the nasal septum, the anus and genitalia, the posterior surface of the scrotum and the forcibly extended palms and soles, is not adequate for the detection of the most important forms of eruptive syphilis.

The classification and identification of secondary syphilids, once they are actually seen, is less difficult than is commonly supposed. For the

details and intricacies of special cases reference must be had to more elaborate texts or to consultation, but certain principles are helpful in ordinary practice. The elementary lesions involved are the macule, papule, pustule, follicular papule or "follicle" and the scar. The presence of vesicles, unless part of an intercurrent ailment, practically eliminates syphilis from the eruptive possibilities. Secondary syphilids of the skin tend to be widely distributed, in accordance with the wide generalization of the infection at this stage. The more or less suggestive groupings are, for the macular eruption, the flanks and abdomen, shoulders, upper arms and back. The papular eruption tends to follow the same distribution as the macular, but with an increased predilection for the face, palms and soles. Pustular secondary syphilids tend to appear on the trunk, face and scalp, especially the latter in the white patient (varioliiform distribution). Follicular syphilids are most frequently seen on the back and arms, and in the scalp give rise to the patchy, moth-eaten spots of thinning of the hair so characteristic of syphilitic alopecia. The commonest type of secondary syphilid is the macular, comprising about 50 per cent of the manifestations of the secondary period. The maculopapular eruption constitutes an additional 20 per cent. The macular eruption is a faint pink, measly rash, the spots being quite uniform in size and quite profuse, though not conspicuous, in the distributions mentioned. Very coarse macules, 2 or 3 cm. in diameter and correspondingly few in number, may occur. The transition to papular elevation can often be seen best in the flanks by a cross illumination, with the examiner standing at four or five feet from the patient. In fact, it is often almost impossible to recognize a macular or maculopapular eruption unless one can inspect the patient from a distance of four or five feet with the arms extended above the head, and with a cross illumination.

The follicular eruptions in syphilis have a useful diagnostic characteristic in the grouping of the little "goose flesh," pinkish papules at the follicle mouths into clumps of fives and tens (this is not, however, an infallible guide). The most important single characteristic of papular lesions in syphilis is their induration when palpated with the flat of the finger. They are of a fleshy, rarely a shotty, feel and give a distinct impression of depth, as contrasted with the mere surface resistance of scaly lesions. Ring-shaped or annular lesions are variations on the papular type, and may either consist of continuous raised rings, as perfectly circular as if drawn with the compass, or of groups of papules (neurosyphilid of Unna) in a ringed arrangement. The diameter of the rings may vary greatly, but they are usually small (1-4 cm.) and most common about the face and neck, especially in the colored patient. They may be concentric or made up of segments of circles. They also occur on the scrotum, where their presence is often of great diagnostic value, though again confusable with the lesions especially of psoriasis and lichen planus.

The rarer syphilids of the secondary period, such as the giant pustular or rupial, are so conspicuous and suspicion-arousing that they seldom escape diagnosis by the blood test. Modifications of the types mentioned, such as the psoriasiform syphilid, must be interpreted by experience and special descriptive aids. Certain rules of thumb are of help in interpreting syphilids of the secondary period as follows:

1. Color, except as an expression of the relative indolence of the

process, which is seldom of a brilliant or glowing red, has little significance for the diagnosis of early cutaneous syphilids. The "raw ham color" and the "copper colored spot" belong to the literature of reformatory and ecclesiastical syphilology, and are more often deceptive than helpful.

2. The papular phase of a macular eruption tends to appear upon the mucous membranes as mucous patches or erosions, and as papules on the palms and soles. The maculopapular eruption tends to be associated with condylomas or vegetative lesions at the flexures and the anus.

3. The follicular eruptions cannot appear upon the palms and soles because in these sites there are no hair follicles.

4. An involuting papular eruption tends to persist longest on the face, forehead and chin and the most dependent parts of the extremities, if they were involved in the original outbreak.

5. Grouping or clumping of lesions and annular or ring-shaped configurations always bring syphilis into the differential diagnosis.

6. The nonsyphilitic cutaneous eruptions most frequently confused with secondary syphilids are pityriasis rosea, measles (mild), variola (mild), lichen planus and psoriasis.

7. A macular eruption with erosions in the mouth and papules about the genitalia suggest syphilis. If there are blisters on the skin, the same association suggests pemphigus or erythema multiforme.

8. A papular eruption on the palms or soles, with nothing on the scalp, elbows and knees, with no fissuring or patches of eczema elsewhere on the body, and without severe constitutional disturbances, suggests syphilis.

9. Freedom from involvement of either mouth or throat, or genitalia in the presence of a general eruption, is against syphilis. In a general papular eruption, this has less weight; and in a pustular or follicular eruption even less, for in these types mouth and genitalia are often free.

10. A marked general adenopathy with an indolent general eruption speaks in favor of syphilis.

11. The association of severe itching with a general eruption is against syphilis. Grouped follicular and psoriasiform syphilids, however, sometimes itch.

12. Rapidly falling hair, even before patches of alopecia are detectable, associated with severe headaches, suggests early syphilis.

13. Sore throat associated with a macular or maculopapular eruption that persists more than a week suggests syphilis before any other possibility.

14. A general eruption, exclusive of vesicular and bullous types, that is accompanied by marked loss of weight is suggestive of early syphilis.

The differential diagnosis of early cutaneous syphilids is at times an elaborate and difficult affair, from which the serologic tests have largely relieved the present generation of physicians. Where these, as later discussed, do not suffice, recourse must be had to consultation or more elaborate treatises.

Mucosal and Mucocutaneous Lesions of Early Syphilis.—The clinical recognition of these lesions, the source of much of the transmission of acquired syphilis from person to person, is one of the most important and most neglected duties of the practicing physician. The shortcomings are not, however, entirely his fault. The mucous erosion or patch

is one of the most fugitive, unobtrusive and least symptom-arousing of all the lesions of the disease. A throat may be absolutely clear on examination, and the following day be the site of a tonsillar mucous patch. A large part of the medical responsibility for the failure to recognize infectious lesions is due to unsystematic and incomplete examination of the mouth and throat, the anus and the genitalia. Here again, an adequate light upon the folds, corners and contact surfaces of the regions involved is absolutely essential. I have seen a nose and throat man livid with rage after a submucous resection. I had just demonstrated to his staff and himself a mucous patch on the underside of the upper lip which he and his internist had overlooked in operating upon a patient with a positive Wassermann reaction. The face of the otolaryngologic confrère had, of course, been spat full of spirochetes. I have watched a medical colleague violently washing his hands, his mouth dry and his face pale. I had just pointed out to him the swarming mucous patch over which his bare index finger had passed a moment before. The electric lamp had hung a little too far forward above the patient to light the fourchet, and the lunette of shadow had been the ambush. An absolutely inveterate habit of prying into orifices, flashlight and tongue blade in hand, is the only guide to the importance and the danger of these lesions in syphilis.

Mucous lesions, including condylomas, are present in from 50 to 60 per cent of patients at first examination during the secondary period of the disease. They are more common in women (75 per cent or more, depending on the use of speculum examination) than in men (55 per cent). Morphologically, the mucous patch is simply a flat papule with the top washed off by moisture and secretions. The contour is rounded, unless modified by situation, as in the angles of the mouth or along the sides of the tongue. The base is eroded, though in the later months of the secondary period the tendency toward destructiveness may result in actual ulcerations. This nondestructive character, the indolent, uninfamed border, and the distinctly pearly, relatively delicate film of exudate that covers the affected surface, is an important differential aid in distinguishing mucosal syphilis from streptococcal, diphtheritic and Vincent's infections. While syphilitic sore throat may vary in severity from the mildest trace of inflammatory engorgement to tremendous swelling and diphtheroid membrane formation, there is usually a striking disproportion between the extent of the process as apparent on inspection, and the mildness of the patient's symptoms. Satellite adenopathy, present as part of the general glandular involvement of this stage of the disease, is usually more pronounced and more tender in other infections than in syphilis. The chief problem is not so much the recognition of the more extensive involvements (though these are often enough subjected to smear and culture to no purpose), but to be invariably systematic enough in inspection of mucosal surfaces to detect the occasional lesions hidden away in folds or covered by the tongue depressor. Special attention must be paid to the commissures of the mouth and the insides of the lips, which are too often looked *past* rather than *at* in the hurry to inspect the throat. The dorsum of the tongue, when involved, usually presents not erosions but flat mosaic or rounded papules from which the papillae seem to have been smoothed away. They are most abundant toward the middle posterior part of the dorsum. Leukoplakia, a silvery or whitish leathery mosaic thickening, dry and

not removable by scraping, in contradistinction to a pellicle, should not be confused with the mucous patch of which it is often the scar-like residue. The silvering of the mucosae by the minute stellate or stippled papules of lichen planus in the mouth, the coarser patches of lichen planus thickening, the leukoplakial changes on the labia in kraurosis vulvae, must be distinguished likewise, and are a source of error to the inexperienced. Syphilis does not give rise to blisters on the mucous membranes; and when either a bulla or its ruptured, sodden remains are found, the possibility of erythema multiforme, pemphigus, and of the barbitol and phenolphthalein drug idiosyncrasies must be carefully considered. The marked fetor associated with the stomatitides of mercury and bismuth intoxication, and the greater involvement of the soggy, bleeding and discolored gums is an important differential aid. The fetor of erythema multiforme and the peculiar livid red of the lips and mucous surfaces in this condition help to differentiate morphologically a condition which is only too often confused with early syphilis.

The genitalia may, both in men and women, be the sites of erosions and mucous patches even on the skin surfaces, owing to the moisture and friction prevailing in the folds and contact surfaces of these parts of the body. It should not be forgotten in interpreting such lesions that phenolphthalein is known to produce genital erosions, and that *ulcus acutum vulvae*, a *Bacillus crassus* infection in women, and serotal and vulvar aphthae and Vincent's infections, also may give rise to erosions and shallow ulcers very puzzling to the inexperienced. The most conspicuous lesion of the genital regions and anus in secondary syphilis is the condyloma developing from the hypertrophy or cauliflower growth of eroded papules. In the flexures about the thighs, scrotum and labia these "flat warts" are easily recognized. But quite the contrary may be said of them when they occur at the anal ring. There the patient's insistence that he has "piles" too often leads to hemorrhoidectomies or other local treatment, dangerous to both physician and public. A hemorrhoid or tag which has a pellicle or eroded surface is a legitimate object of suspicion to the less experienced examiner, and deserves a dark field examination, and always a serologic test for syphilis, together with a careful inspection of other mucous surfaces.

The flat condyloma is syphilitic—the pointed condyloma or fimbriated wart, rarely, if ever, is. Pemphigus, mentioned in connection with mucous patches, also gives rise to condylomatous growths about the genitalia, which spring from the floors of ruptured blisters rather than from hypertrophic papules.

Constitutional Symptomatology of Early Syphilis.—Syphilis is notable for the mildness of the constitutional symptoms accompanying the general reaction against the fully disseminated infection. They may develop within a week after the appearance of the chancre. On the other hand, approximately 50 per cent of patients have no constitutional symptoms whatever, even at the height of their eruptive stage. Women are more often affected constitutionally than men (63 versus 42 per cent), for unknown reasons. They are notably more often affected by the combination of anorexia, slight weight-loss, slight anemia and cough with or without slight fever, which leads to mistaken diagnoses of early tuberculosis. The arthralgias and headache with angina lead to diagnoses of "rheumatism," especially in men. In general the symptomatology of early syphilis does not have a striking and clear-cut iden-

tity, as will be apparent in Table I, from a study by McFarland and the writer.²² None the less it may be said that if every physician would investigate the combination of sore throat, malaise and headache persisting for more than a week by a serologic test for syphilis and an inspection of the body surface, a huge amount of syphilis would be nipped full-blown, if not in the bud.

TABLE I.—SYMPTOMATOLOGY OF EARLY CONSTITUTIONAL SYPHILIS

	Per Cent		Per Cent
Sore throat.....	53	Iritis.....	3
Malaise.....	42	Vaginal discharge.....	3
Headache.....	24	"Anemia".....	2
Loss of weight.....	18	Deafness.....	2
Fever.....	14	Hoarseness.....	2
Meningismus.....	8	Myositis and myalgia.....	2
Gastro-intestinal symptoms.....	7	Nocturnal ostealgia.....	2
Rheumatism.....	7	Periostitis.....	1
"Neurotic" symptoms.....	5	Arthritis.....	1
Bone complaints.....	5	N. VII palsy.....	1
Pseudotuberculous symptoms.....	5	Insomnia (essential).....	1
Nervousness.....	4		

The structural involvements of early syphilis are of wide range, and in their extensions and complications constitute so large a part of the disease panorama that they are separately considered under anatomic groups. Certain symptoms, however, of multiple origin, should be summarized here. The *headache* of secondary syphilis is either a diffuse cephalalgia of unknown cause, an occipital type with occasional stiffness of the neck which is an expression of meningeal involvement of the nervous system, or rare localized periostitis giving rise to spot-like pain. The traditional nocturnal character, while suggestive, is often absent and is overstressed in diagnosis. *Gastro-intestinal symptoms* may be due to the rare, acute syphilitic gastritis; be part of the anorexia of a constitutional infection; or be severe and associated with an early acute syphilitic basilar meningitis. *Arthralgias, myalgias*, and the highly localized periostitis of long bones, most often affecting the tibia, form a rather ill-defined and infrequently differentiated group. The *periosteal lesions* of this stage are notable for two things: an extremely sharp, localized point of exquisite tenderness over the swelling, and the frequent report of negative x-ray findings. *Joint involvement* is uncommon, marked by low-grade or insignificant objective changes, an unusual retention of mobility and exaggeration of symptoms on rest with relief on movement. Exostoses, hydrarthroses, bursitis, tenosynovitis, and myopathies, including especially the spectacular syphilitic contracture of the biceps, are among the rarities of the disease as now seen.

The *lymphatic system* in secondary as in primary syphilis shows marked involvement, and the presence of a general adenopathy, with often visible enlargement of the cervical nodes, may furnish a clue on sight as the patient enters the examining room, or be the sign that leads to closer search for confirmatory evidence. The epitrochlears rarely escape, though their enlargement can hardly be given pathognomonic weight. In fact, in some highly refractory or precocious cases, lymphatic reaction may be conspicuously lacking. The lymphatic enlargement is more conspicuous in the negro than in the white person, and

in the former may at times be suggestive even of Hodgkin's disease or lymphoma. Recent studies by Saleeby and Greenbaum²³ have tended to indicate that reduction of the *Spirochaeta pallida* to the granular stage with phagocytosis by lymphocytes takes place in the lymph nodes. Lymphangitis may occur in visible sites and may be mistaken for phlebitis. The *spleen* enlarges to the point of being recognizable by palpation in 36 per cent of patients with secondaries, according to Wile and Elliott.²⁴ The *liver*, no doubt always affected to some extent with the generalization of the infection, gives rise to symptoms comparatively rarely, and these usually only in the form of slight painless enlargement with a tinge of yellow to the sclerae and skin, and bile in the urine. The differentiation of liver lesions is more fully discussed later on account of its relation to treatment. Acute syphilitic hepatitis or icterus gravis, is an interesting, rare and extremely serious complication often terminating in acute yellow atrophy. The *kidney* showed actual changes, as judged by the urine, in 7 of 89 cases studied by Kolmer and Klauder.²⁵ Acute syphilitic nephritis is a rare complication of the secondary period, usually appearing early in, or even before, the eruption and characterized by marked edema, even anasarca, with weakness and anemia, and a urine like that of an eclamptic, which almost boils solid on heating. Little or no blood is present, and these two facts together distinguish the urinary picture from acute mercurial nephrosis, now becoming rare through the increased popularity of bismuth. The syphilitic process responds strikingly to arsphenamine. Later nephroses of similar character are less likely to be syphilitic, and more apt to be due to treatment.

The *eye* has been very interestingly shown by Brown and Pearce²⁶ to be one of the defense structures in the syphilis of rabbits. It is relatively much less important in man, symptomatically at least, at the secondary stage. *Iritis* is the principal lesion, occurring between the sixth month and the second year, and marked by pain, adhesions and bulging (iris bombé) and marked circumcorneal injection. Miliary papular reddish elevations along the inner iris margin are usually syphilitic. The fixation of the pupil by adhesions will lead hurried examiners to suspect nerve changes. In severe papular secondary eruptions on the skin, papules may also appear on the conjunctiva, especially at the inner canthus. Interstitial keratitis in conjunction with secondary lesions in patients having chancres of the lid has been noted as an excessive rarity. The *ear* may be involved by an acute syphilitic neuritis or labyrinthitis, both serious, and the former leading usually to complete deafness unless properly treated. Reactions precipitated in eighth nerves showing early involvement (symptoms of tinnitus and sometimes vertigo) by the premature administration of an arsphenamine may lead to total deafness.

The *blood-forming organs*, as might be suspected from the early localization of the *Spirochaeta pallida* in the bone marrow and spleen, may be markedly affected in the early stages of syphilis. On the other hand, possibly because of the early use of arsenic and the present-day shift from the comparatively hemolytic mercury to the nonhemolytic bismuth, the modern infection is seldom seriously complicated in this way. Sudden drops of hemoglobin occur in syphilitic nephritis and may also be an isolated warning of relapse or the only sign of the disease in the woman. The blood picture is secondary in type, but the much more serious anemias of late syphilis show a marked tendency toward primary

characteristics. The leukocyte count ranges between 10,000 and 20,000 and there is, according to Hazen,²⁷ a relative and an absolute increase in lymphocytes, which in a case in my experience amounted to 65 per cent and led to a diagnosis of early lymphatic leukemia.

The early manifestations of cardiovascular and neurosyphilis and the technic of their detection, are, because of their extreme importance for the later course of the disease, taken up as units in special discussions.

The Latent Phase of Syphilis.—Latency, punctuated by relapse and terminating in the sequelae of degenerative change, is as nearly a ten-word summary of the course of syphilis, from the secondary period on, as it is possible to write. Latency is a spontaneous affair, a state brought about by the defense mechanism of the body, even without treatment, and subject to fluctuation with the action and reaction of tissues and spirochetal foci upon each other. Like the famous title, "All Quiet on the Western Front," it covers in reality every form of warfare characteristic of the disease. While the miliary lymphocytic foci in the aortic wall are fighting the trench warfare of fibrosis, here and there a "putsch" due to a drop in local tissue resistance results in a breaking through of organisms and a temporary revival of spirochetemia from some impromptu "chancre" in the viscera. Then may follow the infection of a fetus, an outburst of delayed secondaries, a revival of some cutaneous form of relapse on skin or mucosae, a blood Wassermann or precipitation test coming positive after a period of negativity, a slight anemia, a dropped eyelid, an infected marital partner without a genital lesion to explain it. The obvious obligation of the physician in such a state of affairs is to maintain as nearly complete, continuous and all-seeing supervision as possible within the limits set by the patient's temperament and circumstances. The earlier evidences of a breach in latency are more serious for the public health. The later ones are, as they approach the stage of degenerative change and allergic reaction (*Umstimmung*), increasingly serious for the individual. The duration of so-called asymptomatic latency may range from, say, the end of the first or second year, to the fortieth or even more than the sixtieth year of a long, active, outwardly healthy and useful life. The guide to the detection of the asymptomatic latent state, the positive blood serologic test, is too often thought of as a symptom rather than a guide post. It is proper to emphasize here and repeatedly later, that a positive Wassermann reaction is not necessarily a lesion. There is enough evidence of its absence in persons who are dying of syphilis, of its presence in persons in lusty good health, and of its value and significance as a sign of resistance to the disease, whose too-ready reversal is of unfavorable prognostic significance, to justify a certain amount of under- rather than over-emphasis of its significance in latency. Latency is significant practically in many other ways. Its duration in the past serves as a guide to the risk of infectiousness. The shorter the period that has elapsed since the onset of the disease, the more spurious the surface calm, the more probable is it that the patient is an active carrier and transmitter, and that evidence of this rôle will be found upon him which may be controlled by treatment. The longer the duration of the latency, the less likely infectiousness; and the later in an average lifetime that latency is discovered, the more cautious the individual prognosis but the more likely to be good. For example, a man whose latency has endured forty years and who is still in excellent health and negative to examination, at

the age of sixty, is probably past the risk of serious complications unless from the rupture of some unrecognizable miliary lesion of a capillary wall. His life-expectancy will hardly permit the disease to overtake him in the time still remaining to him. On the other hand, the detection of a latent infection of five years' duration in a man of thirty involves an element of the problematic that cannot be met by any diagnostic device at present available. He has years, decades, in which to develop lesions whose onset it is impossible to recognize at the time his infection is identified by the accident of a serologic test. Bruusgaard has traced in a most interesting way the outcome or, in a sense, the biologic course of syphilis in the lives of 473 patients under observation, of whom 164 died. Of 304 examined from three to forty years after infection, 27.7 per cent were clinically and serologically negative; 14.8 per cent were asymptomatic but had positive blood Wassermann reactions; 14.2 per cent of the 473 patients had syphilitic disease of heart or blood vessels; 2.76 per cent had paresis and 1.27 per cent had tabes. It is evident that the culmination of latency in cardiovascular disease is the overshadowing risk, beside which neurosyphilis, important though it is, takes second place. That many persons once past the period of secondary manifestations and the recurrence of infectious lesions (first three years) live out practically normal lives, but little affected, if at all, by their syphilis, is an undoubted fact. Just which patient, of those who daily pass before us, will be selected for this happy course and outcome is an affair that remains in the lap of the gods.

Up to this point it has been possible to discuss syphilis as a disease panorama, unrolling itself before us as a definite succession of events, susceptible of narrative description. From this point on a scattering of manifestations occurs which necessitates now a biologic, now a structural, now a therapeutic point of view for interpretation. Accordingly, it seems wisest here to take up the diagnostic tests and the principles of treatment in advance of the discussion of relapse, of infectious recurrence, and of the special description and diagnosis of individual early and late lesions. Without a presentation of the newer diagnostic technique, much of the practical significance and fundamental groundwork of the clinical side of syphilology, both early and late, is missed.

BIOLOGIC TESTS FOR SYPHILIS

The Dark Field Examination.—In discussing the *Spirochaeta pallida*, it was pointed out that the organism is feebly resistant to disinfecting agents, and that its differentiation morphologically from other spirochetes which resemble it depends more on living than on stained characteristics. These two facts have compelled the modern emphasis on the dark field examination of secretions from the untreated lesion in diagnosis. It has, moreover, been intimated that the organism can be recognized in preparations from the primary lesion of the disease before the blood serologic tests are positive, thus making it possible to institute treatment before the infection has become fully entrenched. The *Spirochaeta pallida* may also be found in mucous lesions about the mouth and genitalia, and in the secretions from condylomas, in large numbers. The presence of an adventitious or saprophytic spirochetal flora in both these types of lesions, however, greatly increases the difficulties of differential diagnosis, even with the help of a method such as the dark field examination, which makes it possible to study the living organism. Compara-

tively little experience is required to distinguish between the *Spirochaeta refringens*, the commonest saprophyte concerned, and the *Spirochaeta pallida*. But the differentiation between the *Spirochaeta pallida* and the *Spirochaeta microdentium* in the mouth, and the *Spirochaeta calligyrum* on the genitalia, is by no means easy and, unless surrounded by proper precautions in the collection of material, may lead to serious mistakes. From a number of sources in the past several years, and from personal experience in the attempt to teach dark field technic to medical students, the writer has become convinced that the use of the dark field as an instrument for the early diagnosis of syphilis has theoretical rather than practical value in the movement against the disease as a public health problem, so long as the utilization of the procedure is left to the initiative and resources of the practicing physician. The necessity for special equipment in the form of sub- or supra-stage dark field condenser or cardioid condenser, which is of relatively little use in other fields of work; the necessity for technical training which can hardly be less than two weeks, and which is readily forgotten or never given in the crowded régime of the medical schools, makes the examination of secretions by dark field an affair for laboratories, clinic centers, and specialists. That it can be developed by public health authorities into a centralized procedure like the identification and culture of the diphtheria bacillus is evident both from the practice of the British Ministry of Health and the recent studies of Mahoney and Bryant²⁸ on the viability of the organism sealed in mailable capillary tubes. Even laboratories and individuals claiming to make diagnosis of syphilis by the dark field examination require supervision, as is evident from complaints with reference to the work of commercial laboratories and the experiences of syphilis clinics which receive diagnoses made in this way by outside sources. The great importance of a dark field examination is therefore conceded and emphasized, but the practitioner is advised to heed the following principles in order to secure trustworthy results.

1. An untreated lesion is extremely important, though not absolutely indispensable to a satisfactory examination. All educational campaigns and antivenereal movements should stress this fact and fight the tendency to self-medication, drug-store prescribing and old-time casual doctoring (indiscriminate cauterization, dusting powders, etc.) which defeat effective dark field work.

2. Every practicing physician should be in touch with a hospital pathologist, or a venereologic specialist, whose work he trusts, and who is properly equipped for dark field examinations.

3. The physician should, if possible, accompany the patient to the specialist or send someone with him who will see that he gets there. Too many are lost on the way.

4. A specimen collected from a thoroughly cleaned lesion may be collected in a capillary tube, sealed with yellow vaseline and delivered to the laboratory or specialist, provided the elapsed time between the taking of the specimen and the examination is not greater than 24 hours. The cleaning of the lesion is essential to eliminate saprophytes, and should be done with scalpel, gauze and physiologic salt solution only. Serum rather than blood should be collected.

5. A rubber band around the penis, or 24 hours of saline dressings, may make a dry or treated lesion yield the organisms.

6. Negative dark field examinations by this technic should be sup-

plemented, if direct examination by a specialist is possible, by aspiration of the base of the lesion, or by aspiration of an adjacent enlarged lymph node.

7. While blood for a serologic test should be taken at the first visit, the use of the positive blood test for the identification of a syphilitic primary lesion on which with little trouble an earlier dark field examination might be obtained, is unpardonable. It perpetuates an infectious focus, and it loses the patient from 25 to 35 per cent of his chance for complete and lasting "cure."

8. The collection of 0.2 cc. of chancre serum is sufficient for the so-called "local" Wassermann test, if there is a laboratory at hand which is prepared to do it. The test is positive earlier than that on the blood. It is an adjunct to, not a substitute for, the dark field examination.

9. Dark field examinations on lesions of the mucosae and on condylomas must be interpreted by experts.

10. The highest efficiency of the dark field examination occurs within the first two weeks of the primary lesion, and in an even shorter period for more superficial lesions. The shorter the duration of the lesion prior to examination (*i.e.*, the fresher), the more significant a negative finding. But no negative dark field examination, in and of itself, even if repeated, fully eliminates syphilis from the diagnosis. At least three repetitions in a favorable case are desirable, at two-day intervals, with saline dressing.

11. The *Spirochaeta pallida* cannot be demonstrated ordinarily by dark field examination from dry secondary lesions, from the enlarged lymph nodes of the secondary (not the primary) period, or from the late lesions of syphilis. Dark field examination is, however, important in the recognition of relapse and recurrence.

12. A negative dark field examination should invariably be supplemented by a serologic follow-up. Physicians who possess dark field equipment are referred to the special works²⁹ for discussion of dark field technic in its application to syphilis. Valuable methods for the prompt identification of *Spirochaeta pallida* in selected tissue sections have been developed by Warthin and Starry.³⁰

Blood Serologic Tests—General Principles.—Few phases of modern syphilology contain within themselves more elements of interest, medically and humanly, than the serologic tests for syphilis. The struggle between clinical and laboratory interpretation, the battle of syphilologist and serologist for supremacy, the war between specificity and sensitivity, the slow and difficult development of control in the older test, the rapid rise of flocculation procedures with their lessened expense and increasing accuracy, the impending triumph of simplification in precipitation, —all have unmistakable hallmarks of drama. It is impossible here to present in detail the mechanism of serologic tests from the technical and immunologic standpoint. The following résumé is, however, of value in interpreting the clinical bearings.

Procedures of the complement fixation type (the so-called Wassermann reaction and its modifications) are dependent on the interaction of two systems of reagents, the antigenic and the hemolytic. The hemolytic system, used merely as an indicator of the presence or absence of unfixed complement, has always been a source of added complexity and expense. It is the notable contribution of the newer precipitation tests, that they attack the problem more directly and seek to recognize the

presence in a given fluid, such as serum, of substances due to syphilis (syphilitic amboceptor) by the physical changes which their presence produces in the behavior of added solutions of lipoids (antigens). The physical mechanism involved has recently been greatly elucidated by the work of Eagle,³¹ who has shown that flocculation or clumping—which makes visible the interaction between antigen and amboceptor by way of complement—is a colloidal change, dependent on well recognized physical laws governing the behavior of suspensions and electrolytes. The amboceptor factor in serologic tests, both of the complement fixation and precipitation types, is apparently a serum globulin fraction. The function of cholesterol in increasing the sensitivity of antigens is apparently the purely physical one of coarsening the suspended particles of the lipid antigen, thus increasing their reactivity with the syphilitic reagin or amboceptor. The gradual clarification of the mechanism of serologic tests has had certain notable practical effects. It has done away with the multiplicity of more or less empirically developed antigens. Wassermann tests which still report cholesterinized and noncholesterinized, acetone insoluble fraction, alcoholic liver extract and other antigens, are now definitely receding into antiquity. The single-antigen test surrounded by proper controls is sufficient for practical purposes, and the energy formerly devoted to elaborate antigen set-ups is now better spent on increased quantitative accuracy through the use of different dilutions of serum. The temperature of fixation remains important, the ice box being productive of greater sensitivity, bordering at times on nonspecificity. The tremendous increase in popularity and efficiency of the precipitation tests, and notably of the Kahn procedure in this country, has all but stamped the field, and led important and influential groups such as the Naval Medical Service, and some of the large state and hospital laboratories, to give up almost entirely the performing of a complement fixation procedure, all reports rendered being those of precipitation tests such as the Kahn. There can be no doubt of the value of precipitation tests, or, perhaps, of the fact that they will ultimately replace the Wassermann type of procedure. In the recent Serologic Conference, held by the League of Nations Health Section at Copenhagen, the general superiority of precipitation tests, and particularly of the Kahn, on the score of both specificity and sensitivity was apparent.³² But there remains a margin of cases and a body of knowledge centered around the clinical interpretation of the older procedure which should not be disregarded. The Conference, which represented the foremost serologic accomplishment of the world, agreed that for the present at least both a Wassermann and a precipitation procedure should be used by all laboratories desiring to achieve the highest degree of accuracy and trustworthiness in their reports.

What the practicing physician desires of a serologic test for syphilis is that it shall indicate the presence of the disease in all persons who have it, and in none who do not. He desires, moreover, that it shall indicate to him the effectiveness of treatment, and that the results shall as far as possible be clear-cut positive or negative, not equivocal, partial or doubtful. It cannot be too vigorously stressed that none of these ideal desiderata has been attained. There is a constant battle on between sensitivity and specificity which cannot be interpreted in the laboratory but must always be decided by the clinician, who alone has

at hand all the evidence in the patient which proves or negates the presence of the disease. An over-sensitive test, "stepped up" by a laboratory enthusiast, gives a host of partial and even strong positive readings that cannot be supported by other evidence of the presence of syphilis in the patient—i.e., they are false. It is now, of course, a truism to say that the serologic tests may be negative, and constantly and repeatedly so, in the presence of indubitable evidence of active and progressive syphilis in the patient. Fortunately, the proportion of such false negatives is steadily decreasing under the technical improvements in the tests of recent years. The false negative and the false positive are better understood than the fluctuating serologic result ("serologic discord" of Sheplar, Lyons and MacNeal),⁴³ in which repeated tests in the same case yield positives, single or repeated, partial or complete, interspersed with negatives in bewildering confusion. Too often the practitioner finds these muddled results occurring not only in the work of a single laboratory, but in checks conducted between two or more laboratories and in combinations of complement fixation (Wassermann type) and precipitation tests. In meeting such situations in practice, the physician must simply cease to expect perfection and realize that there is no such thing as an infallible serologic test for syphilis or one that is fool-proof, regardless of the statements of the originator. Serologic practice varies under a multiplicity of factors, many of which are not as yet even fully understood.

The only recourse in the face of the situation, then, is repetition of tests, constant reference to expert syphilologic opinion in clinic and practice, with every conceivable safeguard in the way of cross-checks and means to prevent mistakes. Neither the positive nor the negative report can invariably stand alone. The partial or doubtful positive by any method should never be given to the clinician as such, but simply reported to him as "Indeterminate—repeat." From the syphilologic viewpoint, then, it is proper to insist that Wassermann and precipitation tests can never stand alone but must always be considered in conjunction with the clinical facts. Serologic reports should not be used as substitutes for painstaking history and physical examination. If laboratory reports and clinical facts differ, and often if they do not, the tests should be repeated, whether positive or negative.

What is essentially a method of repeating the test, with about 18 per cent added "edge" due to the stirring up of the disease, is the so-called provocative procedure. As a rule it takes the form of an injection of an arsphenamine intravenously, followed by daily tests for a week. Not all the tests are likely to be reported even moderately positive, and the result must be interpreted in terms of the clinical aspects of the case. As to practical availability outside of clinic practice, the provocative procedure is of little use. A slower provocative effect, detected by weekly blood tests after treatment is initiated, is also noted in some cases and has confirmatory value, in conjunction with therapeutic tests. The practicing physician has the right to demand that the laboratory shall report his tests in adequate quantitative terms, such as are supplied by the Kolmer and the Kahn procedures, and he has the right to be protected against plus-minuses reported on multiple antigens with uninterpretable details as to ice box, etc. These items are for the expert, clinical or serologic, and the physician should be relieved of perplexity in regard to them.

With respect to the laboratory side of serologic tests for syphilis, no matter how well organized or managed, the following principles apply. The laboratory has the right to ask that a specimen be drawn into a clean and sterile glass tube under aseptic precautions, and that the seal be cork or glass. Not less than 5 nor more than 10 cc. of blood should be obtained. Sticklers for accuracy may wish the specimen to be taken on an empty stomach, with no alcohol ingested in the preceding 48 hours, and that the blood be centrifuged and inactivated at once. It is essential, to prevent error, that labels be legible, affixed immediately and held in place not only by paste but by rubber bands.

No laboratory can maintain an absolutely constant degree of serologic accuracy. It must, therefore, be frequently checked against another laboratory; should run two or more procedures of different types itself; and should, if not actually under the control of a syphilis clinic, work so closely in harmony with one that its reports, daily record sheet and partial positive results are under constant scrutiny and the fire of friendly criticism. The critical activities should, in fact, be on an exchange basis, for the clinician as well as the serologist develops quirks, prejudices and false trends. This elaboration of precaution may seem extreme—but the need is apparent to anyone who has to harmonize the findings of a clinic and a serologic laboratory, and to act as consultant to puzzled physicians confronted by a sheaf of partial positives or of disagreements between different laboratories and different reports from the same laboratory.

In general the laboratory should free itself from recognized sources of technical error—frequently changing technicians, carelessly cleaned and handled glassware, inequalities and shortcomings in refrigeration and incubation, variable and uncertain reagents, insertion into a standard technic of foibles and modifications representing the personal prejudices and experimental investigations of the serologist. Serologic procedure is now at the stage when techniques of known and in fact internationally recognized worth should not be displaced by individual variations unless their superiority is conclusively proven by prolonged and massive research, of which the practitioner need not know or be obliged to interpret the vicissitudes. Such procedures, so far as this country is concerned, are the Kolmer³⁴ modification of the Wassermann test and the Kahn³⁵ precipitation test, and these two should, in the writer's experience and opinion, form the basis of reports intended for present-day general medical consumption.

The Biologic False Positive.—The question of the biologic false positive, occurring in the nature of the case and not through technical failure, is still one for controversy. There can be not the slightest doubt that there has been an enormous elimination of factors tending toward biologic error in the more recent tests. None the less, in spite of assertions to the contrary by proponents and originators, it is well, the writer believes, to interpret with caution results secured on old bloods, bloods that have had contact with cotton stoppers, bloods from patients engaged in or recovering from drinking bouts, bloods obtained under ether anesthesia and in febrile states. The writer still feels that tuberculosis in some of its occult and especially lymphatic forms, subacute bacterial endocarditis, and pernicious anemia tend to introduce elements of biologic error. Kolmer (who unfortunately did not participate in the Serologic Conference) has been very insistent that his procedure elimi-

nates practically all false positives, and the admiration of a skeptical clinician is certainly due him for the great improvement on the old state of affairs which his test has brought about.

Partial Positives.—The meaning of partial positives and atypical tests may be briefly discussed. In the writer's experience all tests have what might be called a nonspecific margin, below which they are uninterpretable and negative in comparison with clinical findings in the case. In this category belongs the 10000 Kolmer (44444 is the strongest possible positive), though Kolmer insists that any degree of fixation in the first tube is a positive. With it I would rate the 012 Kahn (333 being the strongest positive). "Delayed negative," in the older technics, is a doubtful positive. "Anticomplementary" means that the serum destroys complement of itself and the controls come down, making the test useless. A shower of anticomplementary reports means something wrong with the technic. With the Kolmer procedure, anticomplementary tests more often than not turn out later to be positives. It should be recalled that the best laboratories, regardless of the details which they send to syphilis clinics and consultants, or reserve for study, should report such tests "Indeterminate—repeat."

Important Trends.—There are several important trends in the serologic diagnosis of syphilis which deserve the attentive interest of the clinician. The first of these is the rapid simplification without loss of accuracy or sensitivity that is taking place. It is not too much to hope that within a short time the precipitation procedures will make possible a presumptive diagnosis or elimination of syphilis within a few minutes instead of a number of hours. Notable contributions to this end are the slide precipitation test of Kline,³⁶ whose modification for eliminating the diagnosis of syphilis requires only 18 minutes, and the "presumptive procedure" of Kahn.³⁷ The value of such a technic, once its accuracy is proved, for the examination of donors for transfusion in an emergency, and before surgical intervention for example, can be imagined. None the less, the temptation to adopt them without other, including Wassermann, controls should be resisted. The great hope for them lies in the possibility of their absolutely routine application in every medical examination everywhere, the results to be, of course, checked by a fuller serologic study of positive and clinically suspicious cases. The reduction of the accurate precipitation test to the simplicity of a blood count or a urinary examination might well herald a syphilologic millennium. It is a cherished hope, too, that serologic tests may ultimately solve the riddle of detecting neurosyphilis without the necessity for examining the spinal fluid (Hinton).

Clinical Interpretation of Positive Serologic Tests.—As the chief avenue of approach to the question as to whether or not his patient has syphilis, the practitioner should be thoroughly familiar with the proportion of positive results to be expected from the various serologic tests in the various stages and phases of syphilis. Unfortunately, the literature on this question is meager in contrast with the all too voluminous literature of comparison between the frequency of positive results on identical sera obtained from different tests. Wassermann and precipitation tests do not necessarily agree in any given phase of the disease. Studies of this problem in the laboratory of my clinic, by McIntyre and Gilman,³⁸ and by Miller,³⁹ indicate that the highest degree of positiveness of serologic tests, combined with the highest agreement between different

tests (Kolmer, Kahn and Kline), is obtained in untreated secondary syphilis. All reports are in accord in regarding the positive Wassermann and precipitation test in secondary syphilis as a practical test of the sensitivity of the procedure used. Any modern procedure which yields even as high as one per cent of negatives at this stage of the disease is open to serious question. Gilman and McIntyre reported 100 per cent positives and 100 per cent agreement between Kolmer and Kahn tests at this stage, in our laboratory. In primary syphilis, on the other hand, the proportion of positives obtained varies, as has been noted, with the age of the lesion and the type of test used. The older Wassermann procedures yield from 25 per cent positives in the first week of the chancre to 85 per cent positives by the fifth week (Craig).⁴⁰ Gilman and McIntyre⁴¹ found 88 per cent of patients with chancres alone positive by either Kolmer or Kahn tests and found the two tests to agree in 93.8 per cent of the cases. Kolmer³⁴ reported in 1927, on the basis of collected studies from his own and Kahn's laboratory, the comparison between his modification of the Wassermann test and the Kahn test, shown in Table II.

TABLE II

Stage	Cases	Percentage Positives	
		Kahn	Kolmer
		Per Cent	Per Cent
Primary Syphilis.....	24	58	67
Secondary Syphilis.....	6	100	100
Tertiary Syphilis.....	24	54	71
Neurosyphilis.....	20	80	70
Congenital Syphilis.....	30	37	40
Treated Syphilis.....	105	47	44

These relatively high figures for positive tests in primary syphilis may deceive the physician into the belief that the Wassermann detects primary syphilis with sufficient accuracy to make the dark field unnecessary. It cannot be too strongly emphasized that the aim of the physician should not be merely to detect primary syphilis, but to detect it *before the serologic tests on the blood become positive*, at which time the prospect of "cure" is from 25 to 35 per cent better than once the tests have become positive. It is an interesting speculation how long the race between various tests for superiority and sensitivity will leave a sero-negative interval after the first appearance of the chancre. It is not inconceivable that with greatly increased sensitivity, such as Eagle's investigations predict, there may be no such thing as a sero-negative primary stage of the disease, the blood tests being positive when, or even before, the chancre actually appears. For the present, however, it is not a matter for congratulation necessarily that one obtains a high proportion of positive serologic tests in primary syphilis. It may simply mean old lesions and serologic instead of dark field diagnosis.

Serologic Tests in Latent and Late Syphilis.—The incidence of positive serologic tests in latent and late syphilis is difficult of interpretation, because of the prominent part played by the tests themselves in the initial diagnosis of the patient's condition. Asymptomatic latency as a medical condition is really only diagnosed by the positive serologic tests. More-

over, in clinical records such conditions as syphilitic aortitis and aortic regurgitation, or syphilitic myocardial disease are often not recognized as such until the Wassermann test is returned positive. If it is negative, other causes are apt to be assigned. It is only where, as in neurosyphilis, a cross-check such as the spinal fluid examination and clear-cut, indubitable clinical signs can be brought to bear that one has the opportunity to realize that there is a definite proportion of late syphilis which is serologically negative in the blood. It should, moreover, be clearly realized that in the later years of a syphilitic infection, different tests, or the same test taken at different times, or even on successive days, give variable and often totally conflicting results. The sero-positive landmark for late syphilis, comparable to secondary syphilis in the early stages of the disease, is general paresis. Clinically definite general paresis should so invariably be sero-positive on the blood that a technic that gives any appreciable proportion of negative results in this condition needs revision. The serologic confusion that marks the later years of the disease must be interpreted in the individual case, as already intimated, by the devices of adequate history and examination, by repetition of tests by the dark field if applicable (early syphilis only), by provocative procedures and therapeutic test, and by the maintenance within and between laboratories and syphilis clinics of a careful system of controls.

In late syphilis, the older figures indicate that a positive Wassermann test may be expected in from 50 to 80 per cent of cases taken in the aggregate. Kolmer³⁴ finds his test positive in the proportion of cases shown in Table III.

TABLE III.—INCIDENCE OF POSITIVE KOLMER-WASSERMANN REACTIONS IN VARIOUS TYPES OF SYPHILIS

Type of Syphilitic Involvement	Blood Wassermann	Spinal Fluid Wassermann
	Positive Per Cent	Positive Per Cent
Primary, 5-14 days.....	44	
10-14 days.....	75	
3- 4 weeks.....	82	
4- 6 weeks.....	94	
Secondary.....	99-100	
Latent (men).....	90	
(women and children).....	50-80	
Chronic skin and mucous membranes.....	90-96	
Bones and Joints.....	80-90	
Gastric.....	90-95	
Liver and Spleen.....	90-95	
Cardiovascular.....	80-96	
Ear, Nose and Throat.....	70-100	
Iritis.....	100	
Prenatal Latent.....	40	20-40
Prenatal Skeletal.....	70	
Interstitial Keratitis		
Iritis, Choroiditis, etc.....	90-95	
Neurosyphilis Asymptomatic (early).....	85-100	(in early S) 30-40
Asymptomatic (late).....	70-90	80-90
Tabs Dorsalis.....	70-85	96
Primary Optic Atrophy.....	85	95
Paresis.....	98-100	100
Cerebrospinal.....	80-90	95-100

DesBrisay and L¹² using a test distinctly less delicate than those now in vogue but dealing with untreated cases (252), found the relative pro-

portions to be as follows, where all available means toward establishing a diagnosis were being employed (Table IV).

TABLE IV.—PERCENTAGE OF POSITIVE BLOOD WASSERMANN REACTIONS IN TYPES OF UNTREATED SYPHILIS

	Cases	Positive	Per Cent
Visceral.....	18	18	100.0
Latent.....	49	46	93.8
Cardiovascular.....	20	17	85.0
Osseous.....	19	16	84.2
Cutaneous.....	22	18	81.2
Mucous Membrane.....	10	8	80.0
Neurosyphilis.....	114	47	41.2

As to the agreement of different types of tests with the clinical facts, McIntyre and Gilman found that the negative Kolmer or Kahn test agrees much more closely in eliminating than in proving the presence of syphilis. The Kahn test is less sensitive than the Kolmer in neurosyphilis (in our series of disagreements, 10 per cent were Kahn positive, 27.3 per cent Kolmer positive). On the other hand in cardiovascular syphilis, the Kahn seemed the more sensitive of the two. The Kline slide test,³⁵ as sensitive as the Kolmer in cardiovascular syphilis, was, like the Kahn, less sensitive than the Kolmer in neurosyphilis and late cutaneous syphilis. We have learned from experience in our own laboratory, under clinical control, that such generalizations as these are unsafe for complete reliance and that both types of tests should be performed to insure maximum sensitivity and specificity.

The Spinal Fluid Examination.—The hallmark of expertness in modern syphilologic practice, and the greatest single advance in diagnostic syphilology since the Wassermann test, is the application of the spinal fluid examination to the diagnosis of asymptomatic neurosyphilis. It marks the point at which the *laissez faire* syphilology of the protiodide pill and the modern syphilology of infection control, the radical cure and the positive attack on the gravest aspects of the disease, part company. Too often looked on as a fad and the pet of specialists, the fact is now unescapable that examination of the spinal fluid is the only way of recognizing, at a stage when treatment is possible, the 30 to 50 per cent of neurosyphilis in one or another of its numerous masks that constitutes a complication and an outcome of the uncontrolled course of the disease.

The earlier in the course of a syphilitic infection the spinal fluid examination is done, the higher the proportion of abnormal findings. Abnormal spinal fluids are found in the primary stage in from 7 to 25 per cent of the cases. In the fully developed secondary stage, untreated, various reports range from 26 to 78 per cent, with a probable mean about 40 to 45 per cent. In treated and more advanced untreated secondary syphilis, it falls to from 24 to 26 per cent. This may be regarded as the basic minimum of neurosyphilis which is not cleared up within the first two or three years of the disease either by the resistance of the patient or a moderate amount of treatment. It is from this group that the tabes and paresis, the vascular accidents and the multiple manifestations of cerebrospinal syphilis are in the later years recruited.

A very natural and proper question relates to the possibility of detecting this proportion of neurosyphilis by symptoms and signs rather than by spinal fluid examination. The proportion of neurosyphilis in untreated early cases, detected by fluid examination in contrast with symptoms or signs, is 2.3 to 1. At this early stage there are no unequivocal signs. After a year the proportion is 1 to 1.4, and after two years, 1 to 2.5.⁴³ If, therefore, the maximum proportion of neurosyphilis, with the minimum of injury as expressed in symptoms or signs, is to be recognized, spinal fluid examination must be done as early in the course of the disease as possible, and certainly before any abatement of maximum treatment intensity, or any rest from all treatment, is granted. It is therefore an error, of the order of culpable negligence, not to insist upon an examination of the spinal fluid in early syphilis. Should the patient refuse it, his blood is at least upon his own head.

The importance of the spinal fluid examination to the detection of neurosyphilis as an element in general medical and surgical diagnosis, likewise, can hardly be overestimated. The most instructive study of this question in the writer's own experience was that with Brown⁴⁴ on the interpretation of the medical complaint of "stomach trouble" in the patient with syphilis. We found that the syphilitic patient with stomach trouble has a lesion of the stomach or gastro-intestinal tract in only 10 per cent of 200 unselected cases. On the other hand 75 per cent of syphilitic patients who complained of stomach trouble had neurosyphilis, and in 59 per cent of these it was detected or confirmed by spinal fluid examination, though only 44 per cent of the patients had positive blood Wassermann reactions, largely because of previous treatment. Only 10 per cent of the entire series had had spinal fluid examinations as part of any previous examination, though 59 per cent were positive. Seventy per cent of the patients with persistently negative blood Wassermann reactions on the blood, not due to treatment, had positive findings in the spinal fluid.

It is important to note, for reëmphasis later, that the spinal fluid does not invariably indicate the existence of a neurosyphilis, which none the less is present. This is notably the case in certain types of tabes dorsalis, including those presenting Charcot joints and gastric crises, and in the comparatively isolated involvements of vascular neurosyphilis and solitary gumma.

Practical Considerations in Spinal Fluid Examination.—Granted, then, that examination of the spinal fluid is an essential part of the management of syphilis and the only means by which medical responsibility for the prevention of tabes and paresis can be met, what practical considerations are important in its performance? First, for the clinical side, emphasis should be laid on an adequate technic. Much of the disrepute and opposition still involving the performance of the test on the part of both patient and physician is the result of fear of accidents and of bungling manipulation. The procedure is entirely safe if properly done. Accidents, of which the writer has seen four in more than 15,000 tests, arise from the following causes:

1. *Performance of the test on patients who have seriously increased intracranial pressure*, resulting in medullary block. This complication is avoidable through routine examination of the fundus oculi before performing lumbar puncture, if there is occasion for suspicion and by the substitution of cistern for lumbar puncture where markedly increased intracranial pressure due to tumor is suspected.

2. *Breakage of needle before or after entering the canal.* This is prevented by using the modern grades of alloy needles which bend without breaking; by supporting the needle-holding hand against the other hand resting on the back, so that no unguarded movement can be made; by using no force against resistance; by subjecting the needle to a bending strain in all directions each time before it is sterilized; by proper care to avoid corrosion within the needle; by adequate assistance in holding the patient in position during the puncture; and by proper instruction of the patient, if coöperative, so that the back does not straighten during the operation.

3. *Hemorrhage into the canal.* This rare accident, of which the writer has seen only two examples in 15,000 punctures, may result from overpassing the needle point into the venous plexus on the posterior wall of the vertebral body, and perhaps from permitting a patient with a flow of bloody fluid on puncture to move about after the test.

4. *Infection of the canal.* This may arise from unaseptic technic; from passing through infected areas beneath the skin or in the muscle; by transfer of infection from the circulating blood to the meninges. For these reasons it is inadvisable to perform spinal fluid examinations, except in crucial emergency, on persons of low resistance, such as advanced diabetics or advanced arteriosclerotics; in old age (over 60); in persons with florid untreated secondary syphilis until the spirochetemia is controlled; and in persons with acute febrile and possibly blood stream infections, unless absolutely necessary for diagnosis.

In the actual technic of performing lumbar puncture, attention to certain details assists greatly in securing a clean fluid and a comfortable patient. It is possible to perform lumbar puncture on a deaf, dumb and blind person without protest, and eight out of ten patients should not know that the puncture has been made until they are told that it is completed. The essentials to such a humane departure from the ordinary are as follows:

1. *Experience on the part of the operator.* A well done puncture requires tactile experience and judgment.

2. *Proper posture of the patient*—reclining on either side, chin drawn down to knees, pelvis and shoulders in exactly the same vertical plane, and held in position by an experienced assistant.

3. *The fourth or fifth lumbar interspace*, directly in front of the operator, and about two inches below eye level.

4. *A skin wheal with 4 per cent novocaine*, followed up by novocaine of the same strength carried to the depth of $\frac{3}{4}$ to 1 inch.

5. *A careful explanation to the patient* as to what is going to be done and what he will feel—a pin prick, a slight “toothache” sensation, and, rarely, a jar or shock felt for an instant down the leg.

6. *A preliminary hypodermic of 1 grain of codeine* 20 minutes before the puncture.

Prevention of Puncture Reaction.—For the prevention of the headache which follows puncture in 10 to 25 per cent of cases, the following items are important, in the writer's experience:

1. *A Greene or Pitkin pointed needle*; the former with a rounded instead of cutting edge; a point kept sharp by touching up before each puncture—and neither feathered, “fishhooked” nor with a misfit stylet.

2. *The collection of the fluid by a very slow drop from the needle end*—at a rate of about one to two drops per second.

3. *The codeine hypodermic previously mentioned*, and bromides, 15 grains, two to four times in the 48 hours succeeding the puncture. Gen-
nerich pointed out the importance of rest, of relief from anxiety, and of
lying absolutely quiet, in promoting the closure of the puncture wound.

4. *At least two hours spent lying on the face after puncture*, with
two pillows under the pelvis to diminish pressure at the puncture wound,
by placing it above the level of the head.

5. *Adequate instruction with regard to decreased activity*. Rest in
bed for a period of 24 to 48 hours is desirable.

6. *Retirement to bed on the least sign of headache after the rest
period*.

7. *A capsule of amidopyrine*, acetylsalicylic acid and sodium bro-
mide, if the patient must be about.

8. *Rheumatic torticollis* and migraine should not be confused with
puncture headache, which is always relieved on lying down.

9. *Pain in the legs and retention of urine* are the warnings of danger.

Cistern puncture, advocated as free from most of the disadvantages
of lumbar puncture from the standpoint of reaction, is a procedure for
experts. Description of the technic may be found in reports by
Spiegel.⁴⁵ The writer does not advocate it for routine use.

The Time to Do the Spinal Fluid Examination.—The enthusiasm of
the clinician is usually, when confronted with the exigencies of private
practice, obliged to make some compromise with circumstances. Theo-
retically, the spinal fluid of the patient with early syphilis should be
examined just after the third arsphenamine injection, provided there
have been no indications for its earlier performance, such as severe head-
aches, meningismus, or symptoms from the cranial nerves. In practice,
however, the performance of the test at this time is a serious tax upon
the relations of physician and patient, and hence upon the continuity of
the patient's treatment, upon which so much depends. So influential
is reaction to lumbar puncture in defeating the aim of treatment as a
public health measure, that the entire venereal disease practice of Great
Britain's Ministry of Health is conducted without reference to it, on
the score of its discouraging effect upon the attendance of the worker at
clinic. A compromise with the necessities in the individual case can
usually be reached by adopting the following principles:

1. Information on the state of the spinal fluid should be thought of
as part of the preliminary or diagnostic work-up of all patients with
positive blood Wassermann reactions on first examination. Without
the information which it yields, treatment decisions are made in the
dark. If puncture is refused and groping is unavoidable, one should
proceed as if the fluid were abnormal.

2. The state of the spinal fluid must be known before suspending
the treatment of an early case. If it is abnormal, the most serious forms
of neurorecurrence and ultimate grave complications may be expected
to follow a rest period or the stoppage of treatment.

3. No resistant or fixed positive blood Wassermann or precipitation
test can be interpreted or dealt with, without examination of the spinal
fluid. Such tests frequently mean concealed or asymptomatic neuro-
syphilis.

4. The spinal fluid examination must be repeated to determine the
progress under treatment of any patient who has neurosyphilitic in-

volvement. The frequency of repetition must be decided by indications in the individual case.

With the above principles in mind, it seems advisable to recommend that in conditions of ordinary practice the spinal fluid examination in a patient under thoroughly modern intensive treatment should be done, if possible, by the sixth month of treatment, at which time even the slightest abnormality is of significance. Under any circumstances, the spinal fluid should be examined before the first rest interval, at the end of the twelfth to eighteenth month; and an examination as late as this may fail to detect certain cases which may show subsequent relapse. It will, however, identify those cases destined for serious complications unless special treatment methods, such as tryparsamide and fever therapy, are employed.

Interpretation of Spinal Fluid Findings.—The spinal fluid as sent to the laboratory for test should be fresh; should be free from blood cells in gross or microscopic amounts unless such were present in it before its removal from the canal; should be sufficient in amount for all tests (8 to 10 cc.); and should be promptly examined. Colloidal tests in particular are affected by hydrogen ion concentration to some extent, and cell counts, to some slight extent, by standing. The same precautions in regard to container tubes and labeling should be used as with the blood serologic tests.

Blood in the spinal fluid, as a result of puncture, suggests technical error. It is advisable, however, even in a perfect entry, to allow at least 30 drops of spinal fluid to flow from the needle before the collection of the fluid into the first three tubes is begun. The cell count should be made by the laboratory from the third tube.

At the time of obtaining the fluid, pressure, turbidity and color should be noted; but the writer has never personally found pressure of enough significance in syphilologic work to require manometric measurement. In neurologic differential diagnosis it is necessary.

Upon the spinal fluid, four tests should be performed for purposes of syphilologic diagnosis, as follows:

1. A quantitative Wassermann test, on more than one dilution of fluid (0.2 and 1 cc.). The quantitative Kolmer test is in our experience the most satisfactory. The precipitation tests on spinal fluid are still in the investigative stage.

2. A globulin estimation which may be either a Pandy, Noguchi or Nonne for ordinary purposes, but which will probably be ultimately some form of total protein determination.

3. A cell count which distinguishes lymphocytes and polymorphonuclears, if present.

4. A colloidal test, upon which much of the differential prognosis depends. For this purpose the gum tests with benzoin or mastic are preferable to the usual colloidal gold tests, which are well performed by very few laboratories.

The willingness of physicians to accept or to think in terms of spinal fluid reports containing information only on the Wassermann test, and the practice of smaller laboratories in reporting on this basis, cannot be too strongly deprecated. All four tests are essential and act as cross-checks on each other. The quantity of fluid routinely obtained should be sufficient for all four tests (8 to 10 cc.) and reports should be rendered on all. No complications, in the writer's experience, are induced by the

obtaining of a sufficient amount of fluid, provided the patient is one who should have been punctured for diagnosis at all, and provided the fluid is allowed to drip very slowly.

The Spinal Fluid Cell Count.—In the course of neurosyphilitic involvement, the successive elements in an abnormal picture tend to appear in a more or less constant succession which will be used in describing their significance. A rise in cell count or a slight increase in globulin is the simplest form of reaction observed; and the rise in globulin, even more than the cell count, is the most persistent abnormality under treatment, though it is at the same time the most responsive to treatment so far as a reduction in the number of cells or amount of globulin is concerned.

The cell count of the spinal fluid is an index of meningeal reaction; that is, of leptomeningitis. It is, therefore, an entirely nonspecific finding and no diagnosis of syphilis of the nervous system can ever be based exclusively upon a rise in the cell count of the spinal fluid. None the less, in conjunction with other clinical and serologic evidence, even a very slight rise in cells may be quite significant.

The typical cell of the spinal fluid in neurosyphilis is the small lymphocyte as distinguished from the polymorphonuclear leukocyte of other forms of meningitis and early poliomyelitis.⁴⁶ The absolutely normal count ranges from one to three cells but an upper limit of four or five cells may be regarded as within the range of normal. So far as syphilis is concerned, cell counts of from five to ten lymphocytes per cubic millimeter are the very definite beginnings of the abnormal, and cell counts above ten are absolutely abnormal. In the examination of the spinal fluid of persons known to have syphilis and to be either within the first two or three months of the disease or under the influence of treatment, slight increases in cell count are distinctly significant. Thus a patient with early secondaries who, following his first two or three arsphenamine injections, has a cell count ranging from six to ten, is showing distinctly suspicious evidence of meningeal reaction. Such a count demands a subsequent reexamination of the spinal fluid before he is placed on any form of rest interval. Counts of this type are also obtained in the first spinal fluid examination of a treated patient with early syphilis when this is examined from twelve to eighteen months after the onset of the infection. Under these circumstances they cannot be regarded as normal and warn of the possibility that as soon as a rest period is allowed the patient may suffer some form of neurosyphilitic relapse.

The very definitely abnormal cell counts in neurosyphilis range from 10 to 1,500 cells per cubic millimeter and even higher. In the special type of syphilitic leptomeningitis associated with prenatal syphilis, the cell counts may be so high as to resemble those of a purulent meningitis and the large number of cells may produce an actual turbidity of the spinal fluid. The average range of cell counts in active neurosyphilis ranges from 12 to 100, the larger number of the cases falling in the range between 24 and 50. In the higher cell counts polymorphonuclears in small numbers may be present and they are not infrequently present when the spinal fluid examination is repeated at a short interval after a previous puncture or when some direct form of treatment, such as intraspinal therapy, has been employed.

The height of the cell count has a certain prognostic significance, and

it is possible to show quite definitely⁴⁷ that a spinal fluid with a strongly positive Wassermann reaction and a low cell count has a less favorable prognosis than a similar fluid with a high cell count. The cell count is subject to variation after treatment in the form of increases in the count—coming on the second, third and fourth weeks after treatment is initiated and having therefore presumably the character of a Herxheimer reaction⁴⁸—and also to quite marked drops in count induced by treatment, with or without so-called spinal drainage (“Seesaw counts”⁴⁹).

The Globulin Estimation on the Spinal Fluid.—The increase in the protein in the spinal fluid in pathologic processes is presumably another phase of the meningitis and as such is entirely nonspecific in character. It is therefore impossible to prove the existence of a syphilis of the nervous system by an increase in globulin *per se*. The globulin estimation has only a limited diagnostic significance but increasing emphasis is being placed on its prognostic value. It is the last of the four spinal fluid findings to return to normal under treatment and a total protein estimation thus becomes a very helpful guide to the progress of a treated neurosyphilitic case.⁵⁰

The Colloidal Test on the Spinal Fluid.—It is a little difficult for the clinician to realize that the colloidal test, like the cell count and the globulin estimation, is quite largely nonspecific in character and that it is impossible absolutely to confirm or negate a diagnosis of syphilis by this test alone. None the less, the colloidal tests furnish better evidence of the existence and character of a syphilitic involvement of the nervous system than any other of the tests except the Wassermann. In the performance of these tests, whether by the use of colloidal gold, colloidal benzoïn or colloidal mastic, a series of tubes, ten in number in the gold and mastic tests and fifteen in number in the benzoïn test, contain the colloidal suspension, and a series of color or turbidity changes are induced which are expressed by a series of numerals. Thus, an absolutely normal colloidal test with the gold or mastic technic is read as a series of ten zeros, 0000000000. A negative colloidal benzoïn test, on the other hand, may read as a series of fifteen zeros or there may be a change in the middle portion of the series so that it reads as follows: 000,000,033,-310,000. A certain amount of variation from the absolutely zero and negative curve is allowable and a mastic of 1100000000 is regarded as negative.

The two types of the positive colloidal test which are of importance in the interpretation of neurosyphilis are the so-called first- and second-zone, or “paretic” and “luetie,” curves. The so-called paretic or first-zone curve as represented in the numerical form always reads high to the left. In other words, in the colloidal test a typical paretic curve would be 5555432100. In the benzoïn test it reads 333.333.332,100,330. In the mastic test the readings in the first-zone curve may range from 3333321000 to 5555310000. Colloidal tests are capable of expressing a certain degree of intensity of reaction so that a paretic first-zone test may read 2222100000, a curve of much less intensity than one of 5555432100. Such changes may occur under treatment and they are also well known to constitute fortuitous variations in successive readings under varying physiologic and laboratory conditions. The luetic or syphilitic curve, an accompaniment of other forms of neurosyphilis than paresis, reads in all three types of test, “high in the middle and low at both ends.” Thus, a typically intense luetic gold-sol test would read

0124554100. Milder types of this curve would not reach 5 on the middle tubes.

Various atypical curves are observed from time to time in the examination of the spinal fluid of all patients, whether they have syphilis or not, and these variations can only be discounted by experience. Atypical curves may have one or two high digits at the left with marked irregularities throughout the remainder of the series. Tests with no reading above 2 and sometimes even frankly negative tests must be regarded, in accordance with the circumstances of the case, as indeterminate in character and subject to special interpretation.

A third type of curve occasionally seen in patients who have coincident syphilis with other diseases of the nervous system is high on the right, the so-called meningitic curve, which is without significance as regards the diagnosis of neurosyphilis.

It is extremely important to emphasize, in dealing with the colloidal tests, that, like all serologic procedures, they are subject to error and that a single test which conflicts with the clinical facts must not therefore be accepted as gospel. In fact, in labeling a certain type such as Zone 1 as "paretic," emphasis must be placed on the fact that while a paretic curve is invariably of serious prognostic significance, it does not by any means invariably mean that the patient is destined for a paretic outcome. In fact, the interpretation of a paretic curve is sometimes, especially in early syphilis, impossible at the outset and must depend on the repetition of the finding, on its response to treatment and on its relation to other items in the four serologic tests on the fluid in both the original and subsequent examinations. Notwithstanding this necessity for cautious interpretation, the first-zone gold-sol test in its presence or absence is the one most important single prognostic item in the spinal fluid examination with respect to syphilis.

Interpretation of the Spinal Fluid Wassermann Test.—The Wassermann test on the spinal fluid should invariably, as has been said, be performed by some type of quantitative procedure, of which the writer personally can commend the Kolmer. The spinal fluid Wassermann test is the one specific test in the entire series and the only one which points, when definitely positive, directly to the diagnosis of syphilis. It is essential to do a quantitative test because in the spinal fluid the Wassermann reaction may not appear positive until the larger amounts of fluid are employed. This is especially true very early in the disease when the meningeal reaction is the chief pathologic phenomenon and likewise quite late in the disease, when the entire neurosyphilitic process is dying out. No physician therefore should ever be content to receive from the laboratory the simple statement that the Wassermann reaction on the spinal fluid is positive or negative. It is essential in interpreting the prognostic significance that he know on how much fluid within the range of 0.2 to 1 cc. the Wassermann reaction is positive.

As just stated, the Wassermann reaction tends to be negative on the spinal fluid early in the course of the meningeal reaction that develops in from 20 to 50 per cent of patients with early syphilis. This is extremely important, for the nonspecific character of the other tests and the frequent negativity of the Wassermann at this stage, taken together, may lead the examiner to the conclusion that the patient simply has a slight, banal meningitic involvement associated with anything but the neurosyphilis which he actually has. In contrast to this relative in-

significance of the negative Wassermann reaction on the spinal fluid early in the disease, equal emphasis must be placed upon the very great significance of the strongly positive Wassermann reaction on all dilutions of the spinal fluid. It is, of course, possible for technical and nonspecific false positives to occur in the spinal fluid Wassermann test, but they are not common, and the other three checks, together with the clinical aspects of the case, afford important aid in interpreting them. The strongly positive spinal fluid Wassermann reaction is always a serious matter and when accompanied by a first-zone colloidal test is extremely serious, absolutely regardless of the globulin and cell count. The most refractory and unfavorable aspects of general paresis tend to be accompanied by just such fluids with strongly positive Wassermanns and first-zone colloidal tests, low cell counts and low globulin estimations.

Interpretation of the So-called Normal or Negative Spinal Fluid.—The normal spinal fluid typically reads as follows: Wassermann reaction negative on 0.2 and 1 cc.; or Kolmer-Wassermann, 0000; globulin present in normal amount; cell count, 3; colloidal test (gold or mastie), 00000-00000. The normal spinal fluid, while an important index of the absence of neurosyphilis, can never be accepted as absolute evidence that the nervous system is not involved by the disease. Both active as well as arrested neurosyphilis may present completely and persistently negative spinal fluids to all four tests. This is particularly true of vascular neurosyphilis, of those forms of tabes dorsalis associated with gastric crises, Charcot joints and trophic ulcers, cerebral nerve palsies, cerebral gumma, syphilitic epilepsy, Erb's syphilitic spastic paraplegia and non-paretic syphilitic psychosis. As previously stated, it is even possible for the spinal fluid to contain the *Spirochaeta pallida* and yet be entirely negative to all four tests.⁶¹ It may be said, however, in spite of these qualifying remarks, that the negative spinal fluid is better presumptive evidence of the absence of syphilis in the neurologic field than is the negative blood Wassermann reaction in general medicine. It may, moreover, be said that a negative spinal fluid, even in the presence of a neurologic condition, almost excludes general paresis from the diagnosis. The question of the existence of sero-negative paresis is as yet undecided but there are some indications that general paresis in a preponderantly vascular phase may be almost if not quite sero-negative in the spinal fluid, at least after treatment, and yet still be active and symptomatically progressive. Cases of this sort, however, are so rare that they need hardly enter into the diagnostic rules applicable to ordinary practice.

Interpretation of the Positive or Abnormal Spinal Fluid.—Emphasis has already been placed upon the significance of slight grades of meningeal reaction in spinal fluids obtained early in the course of a syphilitic infection, whether in treated or untreated patients. An even greater emphasis in the interpretation of spinal fluid serology should be placed upon what the writer has come to label in his lectures "the red flag." This is the combination of the following findings:

Spinal fluid Wassermann strongly positive on
0.2 and 1 cc.; or Kolmer 4444; globulin ++;
cell count 36; colloidal test 5555431000.

This combination of the strongly positive spinal fluid Wassermann with a moderate or marked increase in cell count, a sharp but not excessive rise in globulin and a first-zone colloidal test, especially when it occurs in conjunction with a strongly positive blood serologic test, is, like the

rattle of the rattlesnake, a warning of something serious to come. This type of fluid is, of course, the earmark of parenchymatous neurosyphilis of the paretic type and it likewise accompanies the so-called neurorecurrence or acute flare-up of neurosyphilis that develops following suspension of treatment when an abnormal spinal fluid has not been recognized by previous examinations. It is impossible to overemphasize to the physician the seriousness of this spinal fluid picture. It is an immediate and unescapable warning that only the most effective and intensive of modern methods of treatment will be of any avail in checking the process going on in the nervous system. Patients who up to this point have been treated by less intensive methods must, upon the appearance of this "red flag," be considered as candidates for tryparsamide and fever therapy unless they make an immediate response to a great increase in the intensity of standard treatment measures. Whenever such a spinal fluid appears, repeated examinations, the first repetition within an interval of three months at the utmost after the first test, are absolutely essential as treatment controls. Once the physician in ordinary practice learns to seek for and properly interpret this "red flag" or warning picture in the spinal fluid, grave neurosyphilis, and general paresis in particular, can be reduced to the level of comparative rarity.

Other grades and types of spinal fluid abnormality include, for example, the meningeal or meningovascular type of early neurosyphilis with beginning parenchymatous involvement and a spinal fluid with a Wassermann reaction perhaps negative on 0.2 cc. but positive on 1 cc. or on the larger quantities in the Kolmer, such as: Kolmer-WaR. 4310; globulin, ++; cells, 101; colloidal test, 0123442000. A spinal fluid with the findings as enumerated but with a somewhat lower cell count is not uncommon in active tabes. In the other types of cerebrospinal syphilis the Wassermann reaction is somewhat more apt to be strongly positive and the cell count apt to be somewhat lower. A spinal fluid report which always seems to be interpreted with great difficulty is the following:

WaR-Kolmer, 0000; globulin, ++; lymphocytes, 17;
colloidal test, 5555421000.

Granted that the blood Wassermann reaction in this case is negative, this is the fluid of so-called multiple sclerosis and is not at all diagnostic of neurosyphilis in spite of the first-zone colloidal test. A mere rise in cell count with a slight increase in globulin and negative Wassermann and colloidal tests occurs as an accompaniment of a good many systemic infections, as Herrick has shown, and must be interpreted in conjunction with the case. Occasionally there seems to be a tendency for partially or weakly positive Wassermann reactions to appear in the spinal fluid of patients with lethargic encephalitis, a fact which is sometimes the source of a good deal of difficulty in differentiation from general paresis. Anticomplementary Kolmer reactions on the spinal fluid and so-called "humpy" Kolmer tests (04021) are sometimes quite difficult of interpretation but usually should be regarded as positive.

It cannot be overemphasized that the spinal fluid examination can never yield its best diagnostic possibilities when interpreted alone. It is part of the general medical and neurologic examination of every patient who has syphilis, and only in conjunction with findings on examination and the coincident serologic tests on the blood can its real significance be evaluated. It is proper, too, to reemphasize the fact that

the blood may be serologically negative and the spinal fluid present definite evidence of neurosyphilis. Accordingly, a spinal fluid examination supplies part of the necessary information for the full interpretation of sero-negative latent syphilis, and of the condition of patients in whom the diagnosis of syphilis, while supported by dark field or clinical evidence, has never been verified by serologic test. Equal emphasis should be placed upon the positive necessity for a spinal fluid examination of all patients whose supposed state of latency has been diagnosed by the strongly positive blood Wassermann reaction. Never, under any circumstances, should a positive blood Wassermann reaction be slurred over or minimized. The least that it demands, once the possibilities of laboratory biologic nonspecific error are eliminated, is an examination of the spinal fluid. Only in this way will it be possible to detect "the red flag" at a time when treatment may yield arresting or curative results.

The Luetin Test.—The value of the luetin test proposed by Noguchi in 1911 as an aid in the diagnosis of syphilis has undergone a number of fluctuations and some discredit since its inception. This has been due, in part at least, to failure to appraise properly at the outset the nonspecific element in the cutaneous allergic phenomena of late syphilis and in part to the fact that luetin tests performed with cultivated *Spirochaeta pallida* do not appear to give as trustworthy results as do those performed with organisms in suspension with tissue extract, such as lung, liver and testis. The revival of interest in the luetin test as a result of the publications of Hollander,⁵² Kolmer⁵³ and various investigators of the Viennese group, including especially Brandt, indicates that the test may have a definite though limited field of usefulness in the future. Kolmer's study of a luetin prepared from heavily infected syphilitic rabbit testis indicated that 33 per cent of 159 Wassermann-positive cases of acquired syphilis, with and without treatment, and 61 per cent of 33 congenital syphilitic patients yielded positive reactions under adequate control. Gandy⁵⁴ in a fuller investigation finds that 10 per cent of patients with primary or secondary syphilis yield positive reactions; latent and late syphilis, 34.2 per cent; and prenatal syphilis, 31.1 per cent positives. Two of seven neurosyphilitics, one of nine cardiovascular cases, gave positive tests. Of the sero-negative latent and late cases, 22.2 per cent gave positive luetin tests; and of the sero-negative prenatal cases, 25 per cent were positive to the test.

It would appear, then, that the test has some confirmatory value as a check upon doubtful serologic reactions in the later stages of the disease and in prenatal syphilitic infections and that it is influenced by treatment. The precise extent of these changes remains to be determined by further experience.

Biologic Tests in Infectiousness and Cure.—At this point in the discussion of syphilis, which marks the transition from the principles of diagnosis to the principles of treatment, it seems advisable to insert for later reëmphasis as necessary a brief summary and discussion of the use of the biologic tests in the determination of the two critical aspects of the disease; namely, infectiousness and so-called "cure."

Blood Tests and Infectiousness.—There are few misconceptions of which it is more difficult to disabuse the practitioner than the feeling that the serologic tests for syphilis determine the infectiousness or non-infectiousness of a given case. Once assured that his blood Wassermann reaction is negative, the patient takes it naïvely for granted that his lib-

erty is restored and that he can once more, from the standpoint of transmission of the disease, comport himself as a well man. Too often the physician, acting under the same misconception, encourages the patient in this delusion. The facts of the matter are these:

1. Infectiousness in syphilis is never determined nor is noninfectiousness proved by the outcome of any serologic test, single or repeated.

2. Noninfectiousness in syphilis is the result of lapse of time and absence of infectious lesions. While the serologic tests tend to become negative with both time and treatment, and tend to be positive when infectious lesions are present, there is no necessary correspondence between the two. The exceptions to the rule are too often the most tragic that can be imagined.

3. The wise physician will therefore allow no relaxation of any precautions which he may have ordered against the transmission of the disease, on the basis of the reversal of a blood test to negative or even of its persistence as negative over a considerable period.

4. He will depend, instead, upon his knowledge of the age of the infection; the peculiarities of the individual case (for there is a definite infectious relapsing type); and on the results of prolonged systematic, empirical treatment with the arsphenamines and a heavy metal; and on frequently repeated physical examinations with special reference to the regions in which infectious lesions are known to appear.⁵⁵

5. In particular, he will never authorize the relaxation of precautions against the transmission of the disease in sexual intercourse merely on the strength of single or repeated negative serologic tests.

The Fixed Positive Blood Test.—The fixed positive blood Wassermann reaction is one of the most difficult interpretative and therapeutic problems of present-day syphilology. While it is impossible to define precisely what a fixed positive blood Wassermann reaction is, one may say roughly, for purposes of discussion, that it is a blood serologic test which remains positive after 20 or more intravenous injections of an arsphenamine given in combination with 20 weeks of intramuscular heavy metal therapy with either bismuth or mercury, or both. The serologic tests may be regarded as persistently positive under these circumstances even though there may have been a brief interval in which the intensity of the positive phase was apparently reduced by the treatment; was subject to fortuitous fluctuation or has even remained, for several tests over a period of a month or so, completely negative. Even though such cases are reduced to negativity by prolonged and intensive treatment, they tend to become positive again at once upon the cessation of treatment, or at times even to gain in positive intensity from a comparatively mildly positive at the start to a strong positive at the close of treatment.

The first concern in the interpretation of pictures such as this is the possibility of an underlying cardiovascular or neurosyphilitic complication unrecognized in the ordinary management of the case. A fixed positive blood Wassermann reaction automatically raises the question as to whether the spinal fluid has been examined. If this has not been done, it must be done before any real interpretation of the findings or of the proper course to pursue can be made. Similarly, the presence of a resistant positive blood Wassermann reaction in a patient under treatment always demands a painstaking physical examination of the cardiovascular system. Unfortunately, the signs of cardiovascular change in such cases may be equivocal or wanting. It is then only possible to tell the patient that repeated examination over a period of years is absolutely

necessary to the interpretation of the situation. In the writer's more recent observation, it has seemed that the blood Wassermann reaction in an obscure and gradually developing, subthreshold cardiovascular syphilis tends toward frequent periods of transient negativity, to fluctuations in positive strength and ultimately even to a complete negativity, some time after treatment is discontinued, while the cardiovascular lesion continues its slow progress. This is perhaps particularly true of the early case and less in the later, fully developed case in which definite physical signs can be recognized.

If there is no evidence of either neurosyphilis or cardiovascular syphilis, the fixed positive serologic finding becomes interpretable either as a "scar" or a defensive reaction. The significance of this state of affairs with reference to the immunologic background of latency and the mistaken treatment of the Wassermann reaction as a disease instead of a symptom, has already had some comment and will be further discussed later. It should also be pointed out that the negative Wassermann reaction is susceptible of relative interpretation likewise. Wile⁵⁶ has pointed out that the increasing sensitivity of modern technics must inevitably lead to an increasing proportion of apparently irreversible positives, complete or partial in character. This is very well illustrated when a service which has been employing a relatively less sensitive technic shifts to one of the more sensitive types, as in the adoption of the Kolmer-Wassermann reaction, for example. It will almost invariably be found that a number of treated patients who were supposed to have achieved a complete serologic negativity will be found positive by the newer procedure. Should one, then, consider that these patients are suffering from a revival or a persistence of their disease? The current biologic outlook upon the situation leaves the question unsettled and simply refuses to accept the negative blood Wassermann reaction under almost any circumstances as complete and final evidence of the extinction of the infection. Under these circumstances, the procedure to be adopted is simply that of complete yearly evaluation of the individual case by the best experience available, with reëxamination and observation continuing throughout life.

Two aspects of the serologic reactions in early syphilis are of very considerable importance. The first of these we owe to the observations of Moore and Kemp⁵⁷ on the so-called serologic gradient. It appears that when the Wassermann reaction is taken weekly throughout the treatment of the early infection, a definite norm for the change from positive to negative can be established. Some cases tend to depart from this in the direction of a more persistent Wassermann reaction and others are comparatively early reduced to serologic negativity. Moore and Kemp succeeded in showing that those patients who fail of a prolonged or at least a typical degree of serologic resistance and who become negative in a short time have apparently a distinctly more marked tendency toward relapse. This easy reversal of the blood Wassermann reaction accordingly becomes a trap for the unwary physician in the early treatment of the disease and a means by which infectiousness is perpetuated through the too-early discontinuance of treatment and through ill-advised assurances to the patient regarding his supposed noninfectious condition while Wassermann-negative. It may be considered a rule of thumb that the patient under standard treatment with an arsphenamine and a heavy metal, whose Wassermann reaction reverses to nega-

tive before the eighth week of his treatment, is showing a positively dangerous degree of serologic response and one which predicates a distinct tendency to relapse or to continuance of the syphilitic process under cloak of a negative serology. A reversal to negative in an early case, nearer the sixteenth than the eighth week, provided the negative persists, is of favorable rather than unfavorable significance for the ultimate outcome.

Emphasis should also be placed upon the great importance of partial positives appearing in the course of a series of negative tests in an early syphilitic patient under treatment and on the appearance of a provocative effect in successive weekly blood tests when treatment is resumed after a rest period. Both of these phenomena, supposing that the partial positive tests are substantiated by adequate control, tend to indicate an impending relapse. This too often takes the very serious form of neurosyphilitic involvement, either when treatment is temporarily suspended or even while treatment is in active progress.

The negative spinal fluid test in early syphilis is subject to some qualifying interpretations from the prognostic standpoint. While as a rule a patient who has a negative spinal fluid at the close of a sufficiently prolonged and effective course of combined treatment is not likely to suffer a recurrence of the disease in his nervous system or even a later involvement, supposing him to have been free at the outset, these rules do not invariably hold. The writer has, for example, seen illustrations of complete, serious hemiplegic neurorecurrence with a typical parietic or "red flag" formula develop in a patient who, after a prolonged and systematic treatment by the most modern methods, had had a completely negative spinal fluid three months before the appearance of the relapse. This negative spinal fluid had been accompanied by months of complete serologic negativity on the blood. It is for this reason that in all patients with early syphilis a second examination of the spinal fluid within a year after the first test and within a year after treatment has been discontinued, is highly desirable, even though the original or first test yielded a complete negative.

How Often Repeat the Blood Test?—In view of these considerations, how often should one repeat the blood serologic tests in patients under observation and in patients under treatment? It must be evident that only empirical rules can be formulated. In the early case the ideal scheme, of course, is the weekly repetition of the serologic test. This, however, is an affair for free clinics rather than for private practice. In theory a serologic test by the eighth and again by the sixteenth week of treatment should provide useful milestones. On the other hand, Colonel Harrison has pointed out a very definite objection to the frequent repetition of serologic tests in early syphilis. The first negative Wassermann reaction constitutes, to the patient equipped with half-knowledge, a landmark in his progress. Too often the information that his blood is negative leads to the prompt disappearance of the patient. The writer has therefore found it advisable, in dealing with certain types, not to repeat the serologic test after the first positive for a period varying from three to six months. It cannot be too strongly emphasized that the treatment of early syphilis, either with respect to duration, dosage, choice of drugs, or predictions as to infectiousness and outcome, cannot be governed by the results of any known serologic test. From the practical standpoint, therefore, apart from the possibility of occasionally

identifying an individual who may tend to relapse, the frequent repetition of blood Wassermann tests during the management of early syphilis tends to overemphasize the importance of the procedure in the eyes of both patient and physician. If the serologic test is repeatedly negative, the patient will tend to regard himself as cured and the physician will tend to abate the vigor of his therapeutic measures. Instead of this state of affairs, the patient should be trained to the knowledge that his blood test is no index whatever either of his infectiousness or his nearness to the goal of cure. The physician, in turn, should accustom himself to the practice of using an empirical scheme of treatment of maximum intensity absolutely without regard to the serologic findings. The important exception to this rule lies in the case of the patient whose blood Wassermann reaction was negative at the time his primary lesion was recognized. In such a case it is desirable to repeat the blood serologic test week after week for several occasions, following the first negative, to be sure that the test does not become positive while the patient is actually under treatment. When this does occur it indicates that the infection at the time treatment was begun was so near full-blown that the more favorable prognostic significance of the sero-negative primary state does not apply. The patient therefore should be treated and observed under these circumstances as having a fully developed infection from every standpoint.

Logically, the most important time for frequent repetition of the blood test in early syphilis is after the completion of treatment and the beginning of a rest interval. Frequent tests during a rest interval, while not tests for infectiousness, are an important method of detecting the threat of both infectious and noninfectious forms of relapse. The blood test should accordingly be used more frequently than it usually is, once treatment in an early case has been suspended, and less frequently while treatment is in progress.

In the fully established latent or late syphilitic infection and the prolonged observational period that should follow the treatment of any early infection, a three-month interval between blood tests is a fair average. Occasionally, even in such a series extending over two years, false positive results may be obtained, to give rise to the most serious misgivings on the part of both physician and patient. When such a situation arises, all the various clinical and laboratory checks that can be applied to the interpretation of blood serologic tests may have to be utilized and it may even, in case of doubt, seem advisable to resume treatment for a time to meet an otherwise uninterpretable and potentially threatening situation.

The closing paragraph of this section should bear home to the practicing physician the fact that no biological tests, either singly or in combination, are able at the present time to establish the fact of cure in syphilis. This does not for a moment discount the value of a long series of negative blood Wassermann or precipitation tests with two or more negative spinal fluids in a patient who has been adequately managed from the therapeutic standpoint. Just as serologic tests in diagnosis can never be satisfactorily interpreted without clinical examination, so they should never be used in a treated case as the sole guides to the arrest of the infection. Clinical observation, reexamination at intervals of a year, with especial reference to signs and symptoms of cardiovascular and neurosyphilitic involvement, are absolutely necessary controls

in the outcome of any case dealt with in accord with modern knowledge. Subthreshold cardiovascular syphilis, the commonest and the most serious of the late manifestations of the disease, capable of progressing to serious damage under the veil of prolonged serologic negativity and defective clinical control by reëxamination, is the Nemesis of the disease today.

THE PRINCIPLES OF THE TREATMENT OF SYPHILIS

Too often the disposition of the student is to avoid a section headed "Principles" and to thumb the pages of a presentation until he reaches the routine prescriptions, systems and schedules of dosage and interval which he fondly imagines will give him the much-desired "practical" knowledge of treatment. No more serious mistake in dealing with the therapy of syphilis can be imagined. The chief defect in our management of the disease today and one reason for the high incidence of complications and the relatively inferior results obtained by the practicing physician lies in his attempt to apply formulas without any conception of the objectives he wishes to obtain, without any conception of the action and purposes of the drugs he is using and the complications he is likely to encounter in their application. The fundamental principles of the treatment of syphilis stand in so close a relation to the biology of the disease that it seems advisable to summarize them at this point before proceeding to the special diagnostic and therapeutic problems in which general principles must be constantly applied.

The time is now long past when any practitioner in any part of the world can use effectively the best methods of his day and generation in the treatment of syphilis. With the development of the arsphenamines and the gradual substitution of bismuth for mercury, with the better understanding and limitation of the use of iodides, with the localizing methods of treatment for special groups of diseases such as the intraspinal therapy of neurosyphilis, and with the rapidly developed technic of nonspecific medication by fever, the treatment of syphilis has made enormous advances. These advances demand of the practitioner who seeks to apply modern knowledge greatly increased skill and a highly specialized acquaintance with diagnostic and therapeutic methods and interrelations as applied to the specific case, such as often only the expert can really hope to possess.

Examine the Patient.—In the good old days, if treatment for syphilis did comparatively little good so far as curative results were concerned, it at least did comparatively little harm to the individual patient. To-day the situation is radically changed. To decide with accuracy and promptitude whether or not a patient has syphilis and to place him on a modern curative treatment are anything but trifling matters from the standpoint of the public health, the welfare of the patient, the possibilities of complications, and the mundane item of expense. Before beginning treatment, not only is it necessary to know with certainty that the patient has syphilis but it is essential to know just what form or forms of the disease he may present and to appraise him, from the standpoint of his possible therapeutic response, and his susceptibility to a wide range of complications. Such an evaluation of the case, the essential preliminary to any and every kind of treatment for any form of syphilis, antiquated or modern, can rest upon only one thing. This is the *adequate examination of the patient*. Even a specialist must

speak with humility when he realizes how frequently he fails to meet the full demands of conscience and sound practice in this regard. If one who devotes his entire time to the problem occasionally trips on some unrecognized though obvious fact in the patient's make-up that could have been identified by examination, how much more frequently must the hard-pressed practicing physician, the specialist in other fields, and the physician who for one reason or another must "take a stab at it," fail to live up to this first and most essential requirement. No matter how a syphilitic infection is recognized—whether by a complaint of falling hair, an accidental or a routine discovery of a positive blood serologic test, a "hot spot" in the family history or a thumping aneurysm presenting through the sternum—the patient must be examined, and examined from stem to gudgeon. Only in this way can we decide what he needs on the basis of what he has, and whether or not he can take it.

Envisage an Aim.—Once having examined the patient and decided upon the full significance for prognosis and treatment of all his findings, the next obligation is to "envisage an aim." We must decide first of all upon the aim of "cure" versus arrest. The objective in a lad of 21 years with a three-day-old chancre is completely different from that in a man of 55 with ataxia, lightning pains and a leaking bladder. In case after case the first decision must be between massive and symptomatic treatment. The most striking contrast exists between the ideals and methods of early as distinguished from late treatment. A selection of drugs and a technic perfectly appropriate to a latent infection with no physical signs to support the positive blood serologic test, may be absolutely fatal if applied to a patient with only trifling aortic signs but the well defined beginnings of an angina pectoris. The mere difference in the spirillicidal effects of bismuth and neoarsphenamine, a matter of less than a week in rate of disappearance of organisms, has been blamed in part for the increase of syphilis in France in contrast with its decrease among her neighbors.⁵⁸ In the modern management of syphilis questions related to the influence of treatment on resistance and the disturbance of defensive balance by injudicious and incomplete therapeutic measures, arise with sufficient frequency to discredit, mistakenly, in the eyes of the inexperienced and uncritical, the entire fabric of the modern and demonstrably effective control of the disease. Let us then definitely agree that it is the first duty of a physician assuming charge of a patient with syphilis to consider with care the best possible objective obtainable for his patient, and to study assiduously the best possible means for obtaining that objective. It is not too much to say that there is a modern technic whose effectiveness can be expected to range from 50 to 100 per cent for the achievement of every practical therapeutic aim in connection with the disease.

System vs. Individualization.—The third general principle reads as follows: "Incline to system early and to individualization late." The whole trend of the modern public health movement against syphilis as an infectious disease is showing with increasing clearness that the treatment of early syphilis can be made a matter of almost hard and fast routine. The comparative youth of the patients, for syphilis is overwhelmingly acquired in the premarital years; their general good health; and, above all, their freedom from the complicating and qualifying disabilities for which syphilis is itself responsible in their later years,

all combine to make the management of early syphilis potentially a machine affair, conforming closely to certain standards and reduplicable from clinic to clinic and office to office practically throughout the world. An entirely different state of affairs, of course, prevails in the later years of the infection. While the sero-positive latent case, in early middle life, may tolerate the therapeutic pounding appropriate to the radical cure objective in the early weeks or months of the disease, the older patient with the handicap of increasing years, a lifetime of struggle, accumulated disabilities and injuries, and above all, the added and grave incapacities induced by syphilis itself, can hardly be expected to endure such therapeutic eudgeling and routinization. It follows, therefore, that two things may properly be expected of every physician who treats syphilis at all. First, he shall systematize his early cases while not neglecting their individual peculiarities; and second, he shall apply the very best individualizing judgment of which he is capable or which he can obtain to the decision as to what is the wisest course to pursue in a patient with a late infection.

A legitimate hope for the future, in this direction, will be the much wider application of the "consultant prescription" to the management of difficult and late or special syphilis. By far the greater part of the treatment of a patient with a syphilitic infection, even under the most difficult circumstances, can be satisfactorily carried out by the practitioner with a reasonable amount of technical knowledge, such as he can acquire in medical school and during his interne contacts. On the other hand, it is unlikely that among the busy demands of practice of other kinds, the majority of physicians can obtain a maximum or even a minimum grasp of the complex of interrelated factors that modify treatment decisions in late syphilis. It is to be hoped, therefore, that foresight, if there is such in medical social planning, will provide advisory centers, better organized syphilis clinics, and adequate, easily available local consultation to assist the practitioner in dealing with his late cases. It is regrettably true that most early syphilis in countries still maintaining an individualistic system of practice is undertreated and over-individualized, while latent syphilis and late syphilis is over-treated and under-individualized.

Risks vs. Benefits.—The fourth principle governing general therapeutic procedure in syphilis might be summarized in the phrase, "Weigh the risks against the benefits."⁵⁹ Elements all too rarely taken into account in therapeutic decisions are, first, the time factor; second, the age factor; third, the impairment factor; and fourth, the tolerance factor. By the time factor is meant essentially the duration of the infection. Where this can be ascertained or presumed, it becomes an important element in the estimation of the required intensity and duration of treatment. On the one hand, for example, the influence of time on infectiousness is highly important. A patient whose disease is of more than five years' duration need rarely, if ever, be treated to prevent infectiousness. It is possible, in such a case, to consider, therefore, only the personal as distinguished from the public health requirements. On the other hand, there is a constant tendency to feel that a syphilitic infection of short duration is more easily cured and requires less treatment than one of long duration. This mistake, which the writer believes is gradually coming to be recognized as serious, was the basis of the concept of abortive cure in early syphilis that has been responsible

for much Wassermann-fastness, relapse, late cardiovascular and neurosyphilis. Many a syphilitic infection of fifty years' duration yields the necessary symptomatic response to the most trifling treatment, while a syphilis of six days' duration may eventuate in almost unconquerable complications, if mismanaged and undertreated.

Consideration of the age factor involves a crude experimental estimation of the rate at which an untreated or partially treated syphilitic infection may be expected to produce symptomatically recognizable complications. Thus, for example, a man of 25 who acquired his syphilitic infection at 18 should be definitely in the period of the disease during which cardiovascular complications are asymptomatic but potentially present. In order to forestall the possibility that some unrecognized complication in this group of structures may later develop, it is, therefore, perhaps advisable to treat this young man of 25 with considerably greater intensity than one of 45 with identically the same clinical and serologic picture. Similarly, a syphilitic infection recently acquired by a man of 65 seems at times to impress the physician as requiring little more than mercury pills by mouth. Yet the problem of the transmission of the disease is not materially different at age 65 from what it is at age 25. In fact, the saying, "No fool like an old fool," frequently makes the adoption of modern spirillicidal and infection-controlling methods a positive public health duty in a patient of 65, more or less irrespective of their effect upon the individual. These are merely examples of the numerous problems involving the biology of the disease and its public health and personal significance which center about the age of the patient.

"Damaged Goods".—Appraisal of the impairment factor, the element of "damaged goods" in every person with a fully established or advanced syphilitic infection, is highly important and sometimes, unfortunately, very difficult. Consider, for example, cardiovascular syphilis. Even a moderate experience with this phase of the disease tends to show that cases may be quite definitely grouped from the standpoint of treatment into those that have and those that do not have a serious grade of myocardial or coronary impairment. It is vitally necessary, therefore, both in deciding treatment and prognosis, to make a specific search for evidence of these two grave complicating elements in the patient who first presents himself with syphilitic cardiovascular disease. Failure to do so may result in shortening rather than extending life expectancy. In late syphilis particularly, a very significant amount of damage, tending to discredit and discourage the use of modern therapeutic methods in early syphilis, has arisen from the failure to differentiate properly the significance of various types of impairment, particularly in visceral syphilis, from the standpoint of their response to treatment.

Tolerance of Treatment.—The tolerance factor will, of course, be taken up in much more detail in connection with the complications of treatment. Commonly neglected items include the history of an irritable skin or of cutaneous complications, evidence of allergic instability, and evidence of renal injury or defect. Even such relatively unusual items as splenic injury or splenectomy, cirrhoses involving the liver and spleen, chronic gastro-intestinal difficulties, are all germane to the estimation of tolerance. On the other hand, it must be said forcibly that only too frequently alleged defects in tolerance of treatment, including

idiosyncrasy, are invoked to explain bad therapeutic results, which in reality are traceable to unfamiliarity on the part of the physician with the intrinsic toxicity and other shortcomings, of the drugs which he is employing in a given case, or even to the absolute contra-indications to their use. It should be more widely understood that there is a way around or a means of forestalling most difficulties in syphilis therapy.

The fourth general therapeutic principle maintains that every physician who undertakes to treat syphilis should know and have on his tongue's end the standard, generally accepted methods for dealing with the condition which he undertakes to treat. This information should come, as far as possible, from authoritative sources, not from single case impressions, from hearsay, or from the too often inadequate or biased knowledge of drug salesmen and detail men. The material is available in the literature and an increasing number of effective and valuable summaries are being published through such vehicles as the special journals and *Veneral Disease Information*, a journal issued by the United States Public Health Service at a nominal price. The systematic efforts now being made by the United States Public Health Service and the Health Section of the League of Nations to evaluate the experience of the important clinical centers for the treatment of syphilis throughout the world, where conditions more nearly approximate the ideal than in the experiences of the individuals too often cited in the pharmaceutical testimonials and leaflets, constitute a notable advance in this field. Their published utterances may well be looked forward to by the profession.

MODES OF ACTION AND COMPARISON OF THE EFFECTS OF THE ARSPHENAMINES AND THE HEAVY METALS

What Does an Arspenamine Do?—Just as in big game hunting it sometimes becomes a matter of life or death whether a confused and excited gunbearer hands his master an elephant gun or a squirrel rifle, so in the treatment of syphilis the whole issue hangs at times, and in fact frequently, upon the opening shot of the campaign and the therapeutic instrument with which it is delivered. It becomes more than essential, therefore, to understand exactly what each kind of shot is capable of accomplishing when one approaches a human thicket alive with spirochetes. The action of the arspenamines, involving as it does not only the individual health of the patient but the entire issue of public health control and ultimate extinction of the disease, should be particularly well understood.

An arspenamine destroys the *Spirochaeta pallida* outright when it is exposed or accessible either in tissues or in the blood stream. This single fact alone explains innumerable disappointments. The ability of the arspenamines to destroy the *Spirochaeta pallida* makes them the modern agents for the control of infectiousness. In fact, the lead in effectiveness and speed of the arspenamines over their nearest competitor, bismuth, which was recently investigated by Levy,²⁰⁰ may be expressed as four to sixteen times. An effective neoarsphenamine in Levy's series caused the disappearance of spirochetes from a surface lesion even in subtherapeutic doses, such as 0.15 Gm., within 24 hours in three out of five patients. With an initial therapeutic dose of 0.3 Gm., in 50 per cent the spirochetes had disappeared within 24 hours; in 38 per cent within two days, and in 12 per cent within three days of its adminis-

tration. Even a water-soluble bismuth preparation could not cause disappearance of spirochetes within 24 hours, the time required being four days in one and six days in eight cases. Inasmuch as mercury is greatly inferior to bismuth as a spirillicide, the obvious superiority of even one of the weaker, though widely used, arsphenamines is beyond dispute. It is, therefore, to the arsphenamines that we must look for our control of immediate infectiousness and hence to our entire public health campaign against the transmission of the disease. It must be obvious, too, that the field of primary importance for the arsphenamines will be early in the course of syphilis, particularly during the first year, during which the original infectious lesions and their recurrences are of greatest frequency. The relative accessibility of the spirochetes during this period of the disease makes it, furthermore, the ideal time at which to use the arsphenamines for curative and preventive effect.

A second striking action of the arsphenamines is their ability to induce rapid healing. It should not be understood from this that healing is tantamount to cure in the treatment of syphilis, for it has been very definitely shown that certain drugs are capable of producing healing without in the least interfering with the progress and increased dissemination of the infection.⁶¹ None the less, this ability to work visible therapeutic miracles makes the arsphenamines extremely attractive to the therapist and gratifying to the patient, and is at times even a danger rather than an advantage.

The arsphenamines have marked tonic properties largely attributable to the arsenical content. They have practically done away with the discouraging and difficultly manageable depressive effect of the older mercurial therapy, with its anemias and hospital pallors, its falling weight curves and intractable anorexias. In fact, the patient receiving an arsphenamine today is in more danger of feeling too well than too ill, and thus too easily discounting his plight and imagining himself the victim of a trivial ailment.

The combined tonic and healing effects of an arsphenamine give this group of drugs an unrivaled therapeutic "push" or curative power. Where the older treatment slowly and laboriously educated reluctant body cells to defend themselves, the newer medication comes upon the field with a dash and a sweep which for the first time in history seems to make the actual extinction of all the organisms possible. Whether absolute cure is possible or not, there is no escaping the enormous increase in power and effectiveness brought into the syphilotherapeutic armamentarium by the arsphenamines. Not by any means all the therapeutic effect of an arsphenamine, however, is due to its ability to destroy spirochetes. These drugs, owing in part to their enormous arsenical content and to other less understood qualities, have marked nonspecific effects which must be constantly taken into account in therapeutic tests. For example, in choroiditis and uveitis due to focal infections, in glandular tuberculosis and tuberculids, in sporotrichosis and blastomycosis, in erythema multiforme, in occasional septicemias, the arsphenamines may accomplish remarkable improvements. These are, however, less pronounced and less lasting than the specific effects. They are brought about in general by small doses and somewhat longer intervals between injections than are commonly used for spirillicidal effects. The utilization of these nonspecific and tonic effects in late syphilis is often of as great importance as the securing of spirochete-destroying action, and is

the basis of the more moderate dosage, longer intervals and repeated, shorter courses that prevail in the treatment of late syphilis.

Certain fundamental dosage principles thus apply to the use of all the arsphenamines. The first of these is that the initial dose should never be more than half the therapeutic dose for the adult. In late syphilis of whatever type it may well be less. At the same time, half the therapeutic dose is too small for routine use in the treatment of the disease. A safe general rule is to use for the adult male two-thirds to three-fourths of the maximum dose prescribed by the manufacturer in the case of arsphenamine and neoarsphenamine, and to increase this proportion with a body weight above the average (150 lb.) and slightly decrease the larger figure for women.⁶² The reduction in maximum dose may then be compensated for by a shortening of the interval between injections from the traditional week to a period ranging from three to five days, if the infection is early; or a lengthening, if nonspecific effects in late cases are sought. The special modification of these principles for particular situations will be subsequently discussed. It cannot be too often reiterated, however, that a uniform application of the maximum dose and a hard and fast one-week interval with neoarsphenamine applied to all cases, early and late, leads inevitably to insufficient treatment of the early case and often over-treatment of the late case; and to this may be added the increased therapeutic complications of the toxic action of the drug as such.

Defects of the Arsphenamines—Allergy and Defense.—Despite their therapeutic value, the arsphenamines have well defined and serious defects entirely apart from their intrinsic toxic actions. The first of these is their general failure to stimulate or reinforce resistance. By their bold and forthright destruction of the organisms of the disease, they deprive the body of its one primordial and essential stimulus to fight the infection on its own account, namely, the presence of the pathogenic agent. The result of an inadequate application of the arsphenamines is therefore at times disastrous. In fact, it is well to impress the patient who has an early infection with the view that his curative treatment is something of an all-or-none affair. If not followed through to a finish, he will be left both without cure and without defense. In the older mercurial days he was left without cure, but with some, though an imperfect, defense. An additional defect of the arsphenamines, appearing in such situations as this, is their tendency in occasional cases, when inadequately used, to leave the patient not only without defense, but in a state of allergic susceptibility akin to the *Umschümmung* of late syphilis. In this allergic state, a relapse induced by his defenselessness against an unextinguished infection assumes grave and often malignant proportions. This is a large part of the background of the severity of neurorecurrence or relapse in the nervous system of the patient with an early infection; and too, of the destructive character of premature late skin and bone manifestations occasionally seen. The patient is literally hurried forward into a precocious tertiarism, or given the appearance of being "arsenic-fast" or absolutely refractory to treatment. It cannot be too strongly emphasized that much of the blame that has been laid at the door of the arsphenamines for the induction of premature neurosyphilis, resistant, destructive lesions and inveterate relapse or Wassermann fastness is the result of the *abuse*, not the *proper use* of the drugs. Too little arsphenamine, especially in the early case, is at times more danger-

ous than too much or even none at all. It is always necessary to carry the drug to a more or less empirical maximum, and to reinforce its action with that of a heavy metal.

Therapeutic Shock (Herxheimer Reaction).—The second effect of the arsphenamines lies in the flare-up of the disease produced by the first or even the first two or three doses of the drugs. This effect, formerly known as the Herxheimer reaction, but better spoken of as therapeutic shock, is one of the most serious pitfalls set for the inexperienced or untrained physician in his everyday use of the arsphenamines. It is not too much to estimate that more than a third of the serious complications of today's syphilotherapy arises from this source. Owing to the rapidity of its action and the rate at which organisms are stirred up and then destroyed in every lesion of the disease by an arsphenamine, a local edema occurs at active foci, which is important in proportion to the site at which it occurs and the severity of the focal reaction. Every lesion of the disease, early and late, be it reiterated, gives rise to a focal reaction to a fast-acting spirillicidal drug such as an arsphenamine. The time of onset may vary from 12 to 24 hours in intravenous medication in an early case to a slowly rising curve of pleocytosis, for example, in the spinal fluid cell count of a late case over a period of several weeks. The reaction may be a visible flare-up of a secondary eruption with a chill and fever, of no great significance for the course of the infection, or it may be an edema of the wall of a coronary artery with occlusion and sudden death.

The prevention of therapeutic shock hinges then, first, upon the adequate examination of the patient to detect in advance of the first treatment any possible focus where a flare-up would be injurious; secondly, on a moderation of the initial dosage so as to avoid explosive effects even if a flare-up occurs; and thirdly, in the absolute avoidance of an arsphenamine and the substitution for it of a slow-acting, relatively nonspirillicidal drug if even a slight degree of therapeutic shock may give rise to disaster. The practitioner through his tendency to employ large initial doses, to fail to appraise completely enough the active focus, and to be unfamiliar with the principles of action of the heavy metals as contrasted with the arsphenamines, too frequently steps boldly into the pitfall to his own discredit and that of really effective modern methods. The procedures for the prevention of therapeutic shock, grouped under the general term "preparation," will be discussed in connection with the heavy metals. It should not be understood that heavy metals never produce therapeutic shock, or that arsphenamines cannot be used without producing it. There is some reason to believe that drugs such as bismuth may produce a very appreciable and even serious degree of shock in some cases, and there is no doubt that the arsphenamines, in suitably low dosage and by a route like the intramuscular which makes for slower absorption, can be used without the induction of an appreciable degree of therapeutic shock.

Therapeutic Paradox.—Closely bound up with their rapid action and their at times too efficient healing properties, is a second defect of the arsphenamines. "Therapeutic paradox" is the term originally applied by Wile⁶³ to this too frequently disastrous action of these drugs in late syphilis. A typical example may be found in the arsphenamine treatment of syphilitic cirrhosis of the liver. The patient with a markedly enlarged cirrhotic liver without evidence of portal obstruction,

if placed at the outset on arsphenamine treatment, will make an initial rapid response with improvement in general condition and marked reduction in the size of the liver. This therapeutic gain, however, is short-lived. The patient presently begins to lose ground, the shrinking of the liver is accompanied by obstruction of portal circulation, ascites develops, and serious complications and an ultimately fatal outcome too frequently ensue. What has happened in a case of this sort is that the arsphenamine, by its rapid healing effects and the fibrosis thus induced, has so seriously interfered with the circulation and function of the liver that by virtually reducing an important viscus to a mass of fibrous tissue it has killed the patient while “curing” the disease. Similar therapeutic paradoxes occur in other situations involved by syphilis, notably in the cardiovascular system. It is essential, therefore, always to weigh carefully the desirability, from the standpoint of future function, of producing rapid healing. A slower reduction of the syphilitic process with less fibrosis, such as could be obtained with mercury and iodide or even with bismuth, would permit compensatory and regenerative adjustment to be made and in the end would conserve vital functional capacity and life expectancy.

“Arsenic Fastness”.—As in the case of other antisyphilitic drugs, it seems to be possible to develop a condition known as true “arsenic fastness.” A recent analysis of the literature by Miller⁶⁴ indicates, however, that failure of a syphilitic infection to respond to an arsphenamine is a function either of the therapeutic inefficacy of the drug or of some peculiarity of the patient which leads him to metabolize it in a way that fails to establish contact, so to speak, with the *Spirochæta pallida*. Outbursts of arsenic fastness in the syphilitic population of individual localities have been reported, notably by Nicolas recently from the vicinity of Lyons, but in such cases the possibility that a widely distributed lot of the drug has been therapeutically ineffective may well be the more probable explanation. There are, however, unquestionable instances in which arsphenamine fails to destroy the *Spirochæta pallida* in surface lesions and therefore presumably elsewhere in the body. Experimental arsenic fastness *in vitro* and in animals has also been demonstrated by Akatsu and Noguchi⁶⁵ and by Klauder.⁶⁶ As a relatively rare defect of arsphenamine therapy it can best be dealt with by using the most reliable drugs obtainable, by not depending exclusively upon the arsphenamines in treatment, and by examining at frequent intervals any spirochete-containing or other visible syphilitic lesion to be sure that normal involution is in progress.

ACTION OF THE HEAVY METALS IN SYPHILIS

The action of mercury and bismuth in the treatment of syphilis stands out best in comparison with that of the arsphenamines, of which they are the logical supplement in present-day treatment methods. Bismuth, to be sure, has a very definite spirillicidal effect as well as an action upon the cellular resistance mechanism in the disease; but this spirillicidal effect is always very much less than that of an arsphenamine and never sufficient to justify the substitution of the metal for an arsphenamine, particularly in the treatment of early syphilis, where spirillicidal effect is at a premium. Mercury, in contrast to the arsphenamines and bismuth, has practically no spirillicidal action when internally administered. While a soluble mercurial salt administered in considerable

doses at very short intervals will cause the comparatively rapid involution of spirochete-containing lesions, the organisms seem to remain active while the lesion is involuting, and the effect seems to be rather upon the body cells than upon the infecting agent.

In the comparative lack of spirillicidal action exhibited by mercury, we find the principal explanation of our failure in the past to conquer syphilis as an infectious disease. Syphilis under mercurial treatment was practically certain to remain infectious for weeks, if not months, and the ordinary and rather expected course of relapses in a considerable proportion of cases often prolonged these episodes of recurrent infectiousness over a period of years. It is evident, therefore, that mercury cannot under any circumstances be considered as the sole dependence in the treatment of early syphilis under a modern régime. Physicians who revert to this practice by the administration of protiodide pills and inunctions to the patient with early syphilis without the employment of an arsphenamine are, consciously or unconsciously, sacrificing the welfare of society to their conceptions of benefit for the individual patient. Fortunately, a proper use of the arsphenamines does away with the objections that have been raised by the ultraconservative group and makes it entirely unnecessary to place the slowly developed resistance and defense mechanism of the patient ahead of the advantages of quick control of infectiousness and development of adequate resistance by artificial means.

Combined Treatment.—It is apparent, then, from the logic of the situation, that the ideal modern treatment of syphilis consists of the combined use of both **arsphenamine** and a **heavy metal** in early and latent cases, and in a suitable adjustment or proportioning in dosage, time and sequence, of the arsphenamines and the heavy metals in the treatment of late syphilis. In early syphilis the question may then be raised as to whether such use of the two types of drugs should be simultaneous or alternate. By simultaneous use is meant the giving of the arsphenamine treatment and the heavy metal treatment in parallel courses, the arsphenamine being given on one day and the heavy metal two or three days later, or both arsphenamine and heavy metal on the same day. It is true that some of the earlier observers objected that this form of treatment put the patient's eliminative mechanism, and particularly his kidneys, under too great a strain. Fortunately, the comparatively low toxicity of bismuth has done away with a large part of this objection. It may now be definitely said that there can be no reasonable objection to the combined simultaneous use of an arsphenamine and a bismuth preparation, and the two may even be given on the same day through considerable series without ill effects.

Where it is desired to adhere to the older practice of administering courses of arsphenamine in alternation with those of heavy metal, a technic known as "overlap" may be employed. That is, the patient, starting treatment with either an arsphenamine or a heavy metal, begins the second course of the alternating drug a little before the end of the first course of the original drug, so that for a brief period of perhaps two or even three weeks he takes both drugs simultaneously. He continues then for a time with the second drug alone; when the first drug is again to be resumed, the course of the second drug overlaps the beginning of the second course of the first drug by another period of two or even three weeks. By this process of overlapping, a certain amount of the

good effect of both alternating and simultaneous treatment is secured with a reasonable compromise in protecting the eliminative mechanism from overload. The further extremely important effect of overlap is to bring about the development of resistance through the use of a heavy metal before the patient discontinues the use of his spirillicidal drug. He is thus fortified against the weak point in arsphenamine therapy and is not laid open to risk of relapse or precocious malignant tertiarism. On the value of the combined treatment of syphilis in securing maximum curative effect and protection from relapse, especially in the early stages of the disease, the writer has been glad to find that his own impression is in accord with the very large experience of Colonel Harrison.

Rules of Arsphenamine Procedure.—From the foregoing considerations, then, with reference to the therapeutic effects of arsphenamine and heavy metals, arise what might be called three great and irrefragable rules governing the employment of the arsphenamine group of drugs in the treatment of syphilis.

Rule 1. Never use an arsphenamine except in conjunction or sequence with a heavy metal, or end a course of treatment with it.

Rule 2. Never use an arsphenamine insufficiently—that is, in a single short course. Either give a long course of the drug or, if short courses seem more advantageous, cover the possibilities of relapse thoroughly by the simultaneous or combined use of a heavy metal. The short single course of arsphenamine, early or late in the disease, not properly combined with or followed by heavy metal, is too apt to give all the disadvantages and none of the advantages of the arsphenamine group of drugs.

Rule 3. Never use an arsphenamine when there is reason to fear either therapeutic shock or therapeutic paradox. Always prepare the way with a heavy metal; always reduce the initial dosage of the arsphenamine to one-half the full or adult dosage, or even less; and do not use an arsphenamine at all in the late case unless it is possible to envisage clearly a lasting beneficial effect.

DISCUSSION OF THE INDIVIDUAL ARSPHENAMINES AND TRYPARSAMIDE

There are at the present time a variety of modifications of the original arsphenamine base available for the treatment of syphilis. It is important to realize the advantages and disadvantages of each and to understand, moreover, that they are not to be lumped together in the mind of the therapist as "arsenic." While arsenic is, of course, the basic constituent which gives these drugs their therapeutic effect, linkage of the arsenic in the molecule of the dye base is the source of their action rather than the mere presence of the drug as such. When this is once understood, there will be less inclination to use cacodylates, Fowler's solution and other arsenical preparations inert with reference to the treatment of syphilis than there has been in the past. A part of the effect of arsenical medication in syphilis is attributable also to the valence of the arsenic. Trivalent arsenicals constitute the spirillicides of the arsenic group; while pentavalent arsenicals, of which tryparsamide is the most notable example, though they have at times striking effects upon certain aspects of syphilis, lack almost altogether the ability to destroy the organisms in the body which is so distinctive and important in arsphenamine therapy. It follows, therefore, that no one who understands the rationale of a pentavalent arsenical like tryparsamide will be likely

to employ it in the treatment of early syphilis except for the one and only indication for which it is fitted, namely, the "red flag" picture in the spinal fluid examination.

The original arsphenamine, Ehrlich's "606," the writer believes it justifiable to say, remains, in the estimation of all those who have had a large experience with it, the paramount drug in the general treatment of the disease in its early stages. Its therapeutic efficacy, as compared with its much more widely used rival, neoarsphenamine, has been estimated as from $1\frac{1}{2}$ to 2 times as great as neoarsphenamine, even in an arsenically equivalent dosage. Unfortunately for the popularization of this extremely effective drug, its preparation for injection requires a rather difficult special technic of neutralization of the solution with sodium hydroxide. When this is not carried through *secundum artem*, a wide variety of vexatious and even very grave complications may follow. This fact has so reduced the general practitioner's acceptance of the drug, and even its popularity in the majority of clinics, that there really is no practical purpose served by describing in detail the technic of its preparation and administration in a treatise of this length. The drug remains now a "pet" of specialists and one which I believe all users familiar with it would select, if they could, for the treatment of their own infections, were they so unfortunate as to acquire them. It should be borne in mind, moreover, that "606" has been the choice of the majority of the larger syphilis clinics of the United States, although it has lost popularity much more rapidly abroad. Accordingly, the greater part of the published material on the results of treatment for early syphilis now available in the American literature is based upon the use of "606."

It must be emphasized that the practice of giving "606" at weekly intervals in courses ranging from six to ten injections each, now usually accepted as the best practice, is by no means to be regarded as the ideal scheme applicable for the weaker members of the series. In leaving "606" behind him, the practitioner or the specialist should divorce himself from the scheme of weekly dosage and comparatively short courses, and take up the short interval, moderate dose, long course systems of combined treatment which are gradually taking the place of the older short course, once-a-week arsphenamine systems. For those who are familiar with the use of "606" from the technical standpoint or who use the ready prepared arsphenamine solution, the writer's suggestion will perhaps be of interest that combined and simultaneous treatment with bismuth is easily possible if the dosage of "606" does not exceed 0.4 Gm. In robust young adults it is possible without any evidence of injury to give "606" series ranging from ten to twenty injections at weekly intervals with simultaneous intramuscular injection of 0.2 Gm. (3 Gr.) **potassium bismuth tartrate** without any evidence of unfavorable reaction. Such a scheme makes possible maximum intensity with prolonged effect and the absence of rest intervals, both of which will be commented on more fully later. It simply applies to "606" the simultaneous injection technic advocated by Schamberg⁶⁷ for neoarsphenamine.

It has also appeared desirable, in the study of the effects of short-course "606," to mass the injections at shorter intervals in the beginning of the course. If the dosage is kept small this is more easily possible and the bad effect of destroying the patient's tolerance by sharp

reaction comparatively early in the series is thus done away with, while the early massive spirillicidal effect is secured. Original arsphenamine ("606") is the drug which lends itself best to the purposes of those who advocate the Scholtz-Pollitzer⁶⁸ intensive system of treatment in which three arsphenamine injections are given within a period of 24 to 72 hours, to be followed by a series of bismuth or mercurial injections before the intensive arsphenamine course is repeated. In offices and clinics in which "606" is preferred, the writer suggests that the best results are obtained by having a technician trained exclusively to its use in complete charge of the preparation of the drug for administration. The art of preparing an arsphenamine, like that of a good cook, is to some extent incommunicable. Arsphenamine solution, when prepared, should stand for 30 minutes to an hour before injection in order that advantage may be taken of the observations of Reid Hunt on detoxification.⁶⁹ Drop by drop neutralization and the one-sixth excess of alkali with a mixture of the monosodium and disodium salts which it produces gives less trouble with the veins and with the patient than does the orthodox quantitative neutralization.⁷⁰ In large clinics the arsphenamine solution should be colored by phenolphthalein, as suggested by Chambers,⁷¹ to prevent accidents; and the drug itself should be marketed in a clearly marked ampule recognizable even without the label.

Neoarsphenamine.—The enormous popularity of neoarsphenamine is due to ease of administration combined with a comparative freedom from immediate and disconcerting complications. Therapeutically the drug, dose by dose, is less efficient than "606." It is, however, about one-third as likely to give rise to exfoliative dermatitis, an advantage which it exchanges, however, for a distinctly greater tendency to produce hemorrhagic encephalitis and aplastic anemia with purpura (aleukemia haemorrhagica). Neoarsphenamine is much more variable than "606" as regards therapeutic effectiveness and it has been clearly shown both by Dale and White⁷² and by Voegtlin⁷³ and his associates that individual lots of the drug on the open market may be absolutely worthless therapeutically even though they may have passed the official toxicity tests and be to all appearances perfectly satisfactory. The Ravaut technic for the administration of neoarsphenamine has become practically universal and involves the simple dissolving of the drug in triple distilled water (now purchasable in ampule) in a concentration of approximately 1 decigram to 1 cc. This solution is nonhemolytic but has the disadvantage of being so concentrated that unconsciously the operator administers the drug with much greater rapidity than he realizes. Inasmuch as this over-rapid administration is the cause of many complications, it should be constantly kept in mind by every user. Important rules for the administration of the drug, whose significance has been brought out both by laboratory investigation and clinical experience,⁷⁴ include the following: no matter how large the clinic or practice, neoarsphenamine should be made up dose by dose, should never be shaken and the nozzle of the syringe should be kept below the surface of the liquid so as not to aerate it. It is the mark of the greenhorn to squirt neoarsphenamine. In contrast to arsphenamine, it should never be allowed to stand. If it does not dissolve almost instantly, it should be thrown away and complaint made to the manufacturer. In its therapeutic use, smaller doses (maximum from 0.45 to 0.6 Gm., the former particularly for women) and shorter intervals (from three to five days)

between injections, with longer courses of 15 to 20 injections each, should be the rule. The drug lends itself particularly well to a combined simultaneous bismuth therapy, the neoarsphenamine being given intravenously in the dosage mentioned on the same day with an intramuscular injection of any of the ordinary soluble or insoluble bismuth salts in full adult dosage. Neoarsphenamine lends itself particularly well to the securing of tonic effects in debilitated syphilitic patients, and nonspecific effects on patients who do not have syphilis, such as, for example, cases of choroiditis and uveitis of focal infectious and other origins. When nonspecific or tonic effect is desired, doses of 0.6 Gm. as a maximum may be given at intervals of one week to ten days. It should be recalled that a dose of less than 0.3 Gm. neoarsphenamine is regarded as therapeutically ineffective from the standpoint of syphilis except in such systems of gradually ascending dosage as have been recommended for the treatment of very late tabes and advanced cardiovascular syphilis.

Sulpharsphenamine.—This drug, studied in this country by Voegtlin⁷⁵ and by Stokes and Behn,⁷⁶ is chemically a near relative of neoarsphenamine and has certain very marked advantages but, unfortunately, certain very important disadvantages. It can be administered intramuscularly in doses as high as 0.4 Gm. and when used in this way is a remarkably efficient antisyphilitic agent. This advantage of intramuscular administration should not be overlooked especially when it is recalled that Ehrlich originally expressed the belief that intramuscularly administered arsphenamines were markedly more effective therapeutically than the same drugs used intravenously. It is also a great convenience in certain cases to be able to give the drug intramuscularly to persons with unsatisfactory veins. The absorption of the drug by intramuscular administration is rapid and satisfactory. The disadvantages of sulpharsphenamine involve a risk of exfoliative dermatitis two to three times as great as even that prevailing with arsphenamine itself ("606"), and at least seven times as great as with neoarsphenamine. Moreover, sulpharsphenamine seems to have a greater tendency even than neoarsphenamine to the production of the highly fatal aleukemia haemorrhagica or aplastic anemia with purpura. The users of this drug must, therefore, be thoroughly familiar with and on the lookout for the two gravest complications of arsphenamine administration. Intravenous use of sulpharsphenamine seems to have no special advantages over the intravenous use of neoarsphenamine.

Neosilverarsphenamine.—This drug has achieved a gradually established position in syphilotherapy and probably exceeds neoarsphenamine in effectiveness though somewhat reaction-producing. The dosage is 0.2 to 0.3 Gm. intravenously, given with the syringe as with neoarsphenamine, and the brown solution must be administered with care to make sure that the entry of the vein has been followed by a proper flow of blood, which is rather difficult to distinguish. Moore in particular has had the therapeutic possibilities of this preparation in early syphilis under investigation.

Bismuth Arsphenamine Sulphonate.—This drug, synthesized by Raiziss in 1925, has had an increasingly extended use in this country for the past six years⁷⁷ and shows a good deal of promise. It is a rational combination of bismuth and a sulphoxalate arsphenamine in one chemical compound and while the dosage of metallic bismuth and of

the arspenamine component is low, the combined effect seems distinctly synergistic and the drug is developing a place for itself. Its advantages include: (1) exclusively intramuscular administration, with comparatively little local reaction, and measurable therapeutic effect in many cases with injections only once a week (though in early syphilis two injections a week are desirable); (2) susceptibility of administration in long courses (40 to 100 injections have been given without a rest interval and with no complications); (3) a very low incidence of complications attributable either to arspenamine or bismuth, which makes the drug a valuable substitute for the other arspenamines when they have set up reaction in a given case; (4) a very high proportion of lasting good effects on the blood Wassermann reaction; (5) low incidence of neurosyphilis under a proper technic in early cases; (6) absence of therapeutic shock and paradox in cardiovascular and hepatic syphilis, provided the initial dosage is very small [0.05 Gm. (0.75 Gr.)]; and (7) ease and simplicity of preparation for administration. The disadvantages include a slower spirillicidal effect than that of neoarsphenamine, though more rapid than that of some bismuth preparations. This delay is sufficient to justify beginning treatment in early syphilis with a more rapid spirillicide such as neoarsphenamine for the first one or two injections.⁷⁸ The drug is not absolutely free from complications and shows possibly somewhat more tendency than neoarsphenamine to give rise to aleukemia haemorrhagica. Jaundice and dermatitis are very rare complications of treatment with bismuth arspenamine sulphonate. Local reaction after injection is sufficient in some cases (8.2 per cent) to compel a change to another drug. The drug is fairly effective against symptomatic late neurosyphilis but practically ineffective against the serologic changes; and hence cannot be particularly recommended for use in this field. In prenatal syphilis the results are still under discussion but have not thus far been striking in the older latent cases. In latent Wassermann-fast acquired cases bismuth arspenamine sulphonate presents no intrinsic advantages not obtainable by varying the mode of treatment with other combinations. It may be said, however, that the drug, in combining both the arspenamine and the bismuth phase of treatment, accomplishes in one motion what ordinarily requires two, with less risk of complications and better general tolerance of a prolonged though moderate treatment régime. The maximum adult dose is 0.2 Gm. (3 Gr.) to be dissolved in 1 cc. of water containing a 2 per cent butyn solution. Care must be taken that the drug is completely dissolved before it is drawn into the syringe, for the presence of undissolved particles greatly increases the reactivity. The drug should **never** be given **intravenously**. The intramuscular technic differs in no respect from that in use for all other intramuscularly administered drugs.

Intraspinal Arspenamine Therapy.--The prominent place held by local treatment of the nervous system with arspenaminized serum, with or without reinforcement by the arspenamines direct, and by less frequently used methods, such as mercurialized serum therapy, is mentioned merely for the purpose of indicating that these procedures are highly special and should not be undertaken by one not thoroughly familiar with them through training and experience, and possessed of the proper equipment. As a matter of fact, intraspinal therapy is very distinctly on the wane and likely to be displaced, except in certain spe-

cial circumstances, by tryparsamide and fever therapy. Intraspinal therapy, all statements to the contrary notwithstanding, is ineffective against general paresis; and its chief field of usefulness is now confined to the treatment of certain cases of low tabes (in which, however, there is a distinct element of risk) and, according to the observations of Moore, to the treatment of primary optic atrophy before the vision has declined below 1/200.

Tryparsamide.—This drug—devised by Jacobs and Heidelberger, and subjected to study by Brown and Pearce, and subsequently by Lorenz, Loevenhart and their associates⁷⁹—is a very important contribution to the treatment of resistant neurosyphilis. It is a pentavalent arsenical with comparatively little spirillicidal effect, and its striking action in syphilis of the nervous system is therefore supposedly due to its remarkable ability to penetrate the meninges and to increase enormously the arsenical content of the brain and spinal cord. Just what the direct mode of action may be, in view of the low spirillicidal efficiency, it is a little difficult to say. It should at least be recalled that the drug is not intended for the treatment of early syphilis. Its field of greatest usefulness in neurosyphilis is that of “the red flag” syndrome or serologic preparesis, and the actual treatment of general paresis itself. There is no evidence at present extant that it has any prophylactic value in preventing neurosyphilitic involvement in early syphilis. The drug is given in what must seem to be enormous doses, 1 to 3 Gm. (15–45 Gr.) once a week, which constitute really a colossal dose of arsenic. Notwithstanding this fact, complications, with the exception of those involving the eye, are very infrequent and in fact almost negligible in practice. The drug occasionally produces slight renal irritation and there have been some suggestions of occasional associated jaundice. Considering, however, the complications attendant upon the intensive use of the arsphenamines, those attendant upon the use of tryparsamide are of small moment indeed. The drug has very marked tonic properties and the constitutional effect upon the patient, if the drug agrees with him at all, is often very striking, including gains in weight, improved sense of well-being and a tendency to increased sexual activity. The drug gives rise quite definitely to therapeutic shock effect and it is usually wise to expect a period of increased disturbance in the irritable or excited parietic, beginning about the third or fourth week after the administration of the drug is begun. While most patients thrive on it, an occasional patient is sure to get very decidedly worse, and if the drug is at all poorly tolerated it is wisest to discontinue it altogether.

The complication of greatest significance in tryparsamide therapy is the **risk of primary optic atrophy**. In the earlier series this amounted to approximately 1.5 to 2 per cent of all cases treated, but the proportion can be very much reduced and in fact made almost negligible by the exercise of the following precautions:

1. A preliminary examination of the fundus and a perimetric test of the visual fields before the administration of the drug is begun, is absolutely essential. Each week after treatment begins, this examination should be repeated on the second or third day after the tryparsamide injection. There is no object in examining the fundus alone, the field test and visual acuity being very much more important.

2. Close account must be kept of the patient's symptoms and a com-

plaint of dimming of vision, grayness, dazzling (as of sunlight on snow), an appearance as of clouds approaching from the periphery of the visual field, and uncertainties in gait (suggesting poor vision), must all be taken seriously.

3. If there is shrinkage of the visual fields, or if the symptoms just described are clearly present, treatment must be at once discontinued. It has been contended by Cady and Alvis that in many cases it may be resumed after 30 days without increase of the field contraction or other injurious effects.

4. The coöperative element in these examinations affects the risk, and patients who are befuddled or whose statements are unreliable become *ipso facto* more subject to the risk of ocular damage because of their inability to report their symptoms adequately.

5. The risk of eye complications is so greatly reduced after the tenth treatment that the eye examination of perimetric fields and visual acuity may be stopped. A check should, however, be kept of symptoms.

Tryparsamide in accordance with the most recent technics⁸⁰ should be given in doses of 1 to 3 Gm. (15-45 Gr.) once a week, continuously, week after week, for periods ranging from one to two or more years. Bunker⁸¹ has pointed out that serologic improvement often does not occur until approximately a hundred injections have been given; but it is wise, none the less, to keep track of the spinal fluid findings at intervals of six to twelve months, especially in patients in whom symptomatic improvement does not serve as a control. The drug is frequently used after a bout of fever therapy and some observers continue to use the original technic of Lorenz, Loevenhart and associates, consisting of ten to twelve injections per course with coincident but not simultaneous injection of mercury salicylate or bismuth. Kemp and Stokes⁸² and Neymann and Osborne⁸³ have used and found advantageous the administration of tryparsamide simultaneously with the height of the therapeutic fever, whether obtained with nonspecific protein or by diathermy.

It is important to realize that the risk of eye complications practically disappears by the eighth to tenth injection. It is accordingly possible to institute treatment under special direction and then to have it continued in the patient's own home by his family physician, an inestimable advantage in all patients capable of remaining at work.⁸⁴

DISCUSSION OF THE HEAVY METALS

In taking up the more detailed discussion of the heavy metals, bismuth and mercury, the fundamental principle of their action, which is less spirillicidal than that of the arsphenamines and more productive of cellular and tissue resistance to the *Spirochaeta pallida*, must be constantly borne in mind. In the practical use of the heavy metals, two additional groups of essential considerations require emphasis. The first of these is the difference in effect of water-soluble and water-insoluble preparations; the second, the effect of route, vehicle and salt employed.

Soluble vs. Insoluble Heavy Metal Preparations.—Since it is obvious that insoluble salts of heavy metals cannot be given intravenously, the following statements apply only to the intramuscular use of heavy metal preparations. Water-soluble heavy metal salts have in general the properties of comparatively quick absorption, rapid action and, because of

their quick elimination, a transient as distinguished from a prolonged effect. Insoluble heavy metal salts, suspended in aqueous or oily media, on the contrary, tend to be stored at the site of injection in what might be called depots, are slower of elimination than soluble salts, and slower in therapeutic action. It follows, then, that to produce a maximum effect of reasonable duration with a water-soluble salt it is essential to administer it at short intervals, say of one to two days. On the other hand, an insoluble salt, because of its accumulation in the tissues, is given much less frequently and for this reason is much more convenient, often in spite of its lessened therapeutic activity. For the securing of rapid but temporary effect, then, a soluble salt of a heavy metal should be chosen; and for the securing of prolonged though slower action, an insoluble salt of a heavy metal is appropriate. It is possible, as in certain preparations, to secure a partial combination of both effects by appropriate mixture of the two types of drugs in the same medium, and by the selection of insolubles which have a fairly rapid absorption and elimination rate.

EFFECT OF STORAGE, ELIMINATION, ROUTE, VEHICLE AND SALT

Studies of the storage and elimination of mercury and bismuth during the past decade have brought out a general rule to the effect that immediately after introduction a relatively rapid absorption of the drug and, for a time, a rapid elimination take place. Not all the drug, however, is eliminated in this first spurt. Practically any form of heavy metal treatment leads to a very considerable accumulation of the drug in the important viscera, in spite of early rapid elimination. The spurt, then, is followed by very slow elimination of minute amounts over a period of many months or perhaps even years. The amounts which thus maintain a pharmacologic action in the tissues may be very small. It appears that for the heavy metal type of drug there is a tissue saturation point beyond which, when once reached, serious toxic manifestations begin to appear. Levaditi⁵⁵ has been particularly insistent on the function of the kidney in the determination of this saturation level of the drug in the tissues and in the blood stream. Just how much of an intramuscularly injected preparation is stored in the tissues about the site of injection is still not fully settled, but there is reason to believe that it is considerable and that the degree of storage *in situ* is not always demonstrable even by such very effective methods as those employed by Cole⁵⁶ and other investigators using the x-ray. The importance of conserving the integrity of the kidney, for which all heavy metals are notably more irritant even than the arsenicals, is apparent from the importance of this structure in maintaining the threshold of saturation and the dividing line between therapeutic and toxic effects. Periodic urine examinations are therefore indispensable in modern practice.

Intravenous vs. Intramuscular Medication.—The writer believes that the tendency to turn indiscriminately toward intravenous as contrasted with intramuscular medication in syphilis, and particularly toward the intravenous use of heavy metals, is one to be deprecated.⁵⁷ The toxic dose of both bismuth and mercury given by the intravenous route is entirely too close to the therapeutic dose; the strain upon the eliminative mechanism and the risk of inducing nephritis is thus so considerable that only a very striking advantage in the way of therapeutic effect would justify it. The writer's experience leads him to believe that there is no compensatory therapeutic advantage to be gained in the

treatment of syphilis by the use of heavy metals intravenously, for every degree of rapidity and energy of action can be secured by an appropriate selection of soluble or insoluble salts for intramuscular use.

Recent investigation points very strongly to the great importance of the vehicle in securing effects from an injected heavy metal. Slowly absorbed oils, even though they carry a water-soluble metal in suspension, interfere greatly with absorption and therapeutic action, while a relatively insoluble preparation suspended in a water menstruum may be comparatively rapidly converted into an albuminate, used and eliminated. The studies of Lomholt⁸⁸ and of Hanzlik⁸⁹ have been particularly illuminating on these points. Levaditi⁹⁰ and his coworkers have emphasized the superior qualities of lipid media on the one hand, and experience⁹¹ has definitely shown the bad effects of suspension of heavy metals in such unabsorbable media as mineral oils, which may give rise even to paraffinomas. Deep intramuscular injection,⁹² as distinguished from subcutaneous injection, seems to constitute the best route, and the more readily ionizable salts appear to be the best utilized. Lomholt⁹³ has indicated that a more complex salt may be eliminated as such without ever being broken up into usable form. In view of the great uncertainties attendant upon these various considerations, particular care is desirable in the clinical evaluation of heavy metal salts. While this is more difficult than the clinical evaluation of the arsphenamines, it should be expected of every manufacturer that a drug which he advocates shall have undergone a prolonged and careful period of clinical trial before it is offered on the market. It is impossible to foresee merely from abstract considerations which preparation will have a maximum therapeutic effectiveness.

Bismuth.—This drug, in use only since 1922, must be reckoned as the most significant item in syphilotherapeutics since the advent of the arsphenamines. It is rapidly replacing mercury throughout the entire field of therapeutic procedure, and while there is sure to be some degree of reaction in time, the very great popularity of the drug seems in the main to be justified. Its combined spirillicidal and resistance-building action makes it more effective alone than mercury for the majority of purposes. It has been questioned by German investigators, notably Kolle,⁹⁴ whether the drug possesses adequate spirillicidal as distinguished from merely bacteriostatic effects, but opinion seems distinctly to be swinging in favor of the importance of the spirillicidal action. Kolle⁹⁵ employed a unique and interesting method of demonstrating bismuth spirochetostasis. The ears of rabbits were injected with a bismuth salt and the rabbits then inoculated intratesticularly with *Spirochaeta pallida*; whereupon it was found that no primary lesion developed and in fact the animal apparently escaped infection. After the incubation period had passed without manifestations, the ear carrying the bismuth depot or "plug" was removed; forthwith the suspended syphilitic infection came to life and a testicular primary lesion appeared. This fact, taken in combination with the now known prolonged storage of the heavy metals in the body, leads to the suspicion that no small part of what we have in the past regarded as their curative effect may be simply the result, as Warthin⁹⁶ has contended, of a prematurely induced and artificially maintained latency or spirochetostasis. In any event, the demonstration of bacteriostatic effects constitutes an additional reason for the

proper use of the heavy metals, and bismuth in particular, in the treatment of syphilis.

Bismuth has earned a large part of its consideration as a successor to mercury through the fact of its notably lower toxicity. It does not produce anemia and gives rise to very little irritation of the kidney. For this latter reason alone it is obviously the more satisfactory preparation to be combined with an arsenical in the production of maximum treatment effects with minimum complications. The chief undetermined questions now outstanding against bismuth are: whether or not the drug sufficiently reinforces tissue resistance to be a complete substitute for the well known effect of mercury in this particular; whether bismuth does not act so fast that it produces therapeutic shock and paradox in gravely involved cases; and whether or not the drug is retained by any mode of administration in a dangerously cumulative degree. Only time can determine the answer to the first question. It must never be forgotten that bismuth, like the arsphenamines, must go through a long evaluation period. With respect to the second question, there is, in the writer's opinion, some evidence that, at least in cardiovascular syphilis, bismuth in ordinary dosage may give rise to both therapeutic shock and paradox, even though in other aspects of the disease its effects on this score are negligible. The question of retention to a dangerous degree is gradually being answered in the negative by the elimination studies already referred to.

Modes of Administration of Bismuth.—In contrast with mercury, bismuth at the present time is administered only intramuscularly and intravenously, mouth administration and inunction being without significant therapeutic effects. The Council on Pharmacy and Chemistry of the American Medical Association has repeatedly emphasized the dangers of intravenous medication, as previously mentioned, and their commendable caution has been supported by the repeated appearance of reports of death following the use of the drug by this route.⁹⁷ Intravenous administration of bismuth is, therefore, not here discussed. The number of preparations, water-soluble, oil-suspended, and liposoluble, available in this country and abroad is legion; and conflicting claims, largely on the part of manufacturers rather than investigators, would seem to make selection extremely difficult. The following commentary is offered simply as a guide to the field. The oldest and hence the most familiar salt in use is the oil-suspended potassium bismuth tartrate. The aqueous suspension of this salt is too irritating for general use. **Water-soluble sodium bismuth tartrate** has recently been strongly commended by the elaborate investigations of Hanzlik and his coworkers.⁹⁸ It should be recalled that such a preparation needs to be administered somewhat more frequently than an insoluble. **Quinine iodobismuthate**, in spite of its relatively low bismuth content (25 to 27 per cent), has had a considerable popularity, in part on account of the tonic effects of the quinine. **Bismuth salicylate** is widely approved and is undoubtedly an excellent preparation. **Bismuth oxychloride** is the present choice of the British Venereal Disease Service (as of July, 1930). A preparation having a very considerable popularity on the Continent and now introduced into this country is a **lipoid suspension** of the water-soluble sodium bismuth tartrate and the water-insoluble quinine iodobismuthate. The investigations of the Levaditi group on **liposoluble bismuth compounds** are leading, as has been mentioned, to

favorable reports of these preparations. The more complex salts, such as the thioglycolate, are not without their advantages. In the welter of conflicting considerations and claims, the writer believes that **potassium bismuth tartrate**, **bismuth salicylate** and the combination of **sodium bismuth tartrate**, and **quinine iodobismuthate**, together with the **water-soluble sodium bismuth tartrate**, meet all the present needs of the practitioner within the field of established knowledge of bismuth as a comparatively new drug. The production of local reaction, which is probably greatest with potassium bismuth tartrate, can be controlled by the use of a local anesthetic in small amounts, and the other preparations named are by any satisfactory intramuscular technic only very slightly irritating. A general dosage rule for bismuth preparations is to administer 0.5 mg. of the metal per kilo per week.⁴⁹ This implies that the bismuth metal content of the preparation chosen must be definitely known, and manufacturers should be expected to place a properly controlled assay of their drugs upon the ampule label.

Bismuth preparations, particularly in the case of insolubles, should be administered in courses with suitably proportioned rest intervals to permit the elimination of the accumulated drug. On the dosage basis given above, a course of 10 to 15 weekly injections should be followed by a rest period of six to eight weeks between the first two courses and if any cumulative effects are observed, by a rest of eight to ten weeks between the second and third courses. In the practical use of the drug, however, these limits are very safe and apparently quite elastic, so that where it is desired to secure a massive or rapid early effect, somewhat larger and more closely spaced initial doses may be used. Hanzlik¹⁰⁰ has, however, shown that overdosage with bismuth leads to a distinct slowing-down of elimination which renders the threat of dangerous cumulative effect more serious. Shortening of intervals between injections in cases of early syphilis should be undertaken only where preparations of known rapid elimination, such as those specifically named above, are employed.

What Bismuth Does Best.—Bismuth fits in with the arsphenamines, so to speak, early and late in the management of syphilis, for its simultaneous use encourages resistance-building at a time when the shortcomings of the arsphenamines in this particular are most serious. Its low toxicity does away with the objections operative in the simultaneous or combined use of mercury and the arsphenamines, and its spirillicidal effect maintains a constant check upon the remultiplication of organisms during periods when arsphenamine treatment must be suspended. Thus it should, at least theoretically, be possible to keep the early case of syphilis, by the use of bismuth as distinguished from mercury, in a non-infectious condition throughout the entire progress of the "cure."

The second accomplishment of bismuth is as a preliminary to the use of the arsphenamines where there is some fear of therapeutic shock following the initial administration of the stronger drug. So satisfactory is the slower and yet effective action of bismuth in this particular, and so free from undesirable complications, that it may almost be offered as a general rule of procedure that wherever involvement of the nervous system in early syphilis is suspected, and in all cases of late syphilis except cardiovascular and hepatic disease with risk of paradox, bismuth is the proper opening and arsphenamine should be temporarily postponed. The rapidity of action of bismuth is such that a period of from

two to six weeks constitutes an adequate preparation for most purposes, which is materially shorter than that required for the slower-acting intramuscular mercurials and mercury inunctions.

Bismuth is a valuable alternate in all cases of intolerance to either arsenic or mercury. Where arsenical by-effects in the skin have interfered with treatment, as in exfoliative dermatitis, bismuth becomes the next best choice. On the other hand, where the continued use of mercury threatens renal injury, a rest period followed by the substitution of bismuth does away with the difficulty. Since the advent of bismuth it has become possible to treat with some semblance of efficiency the relatively rare cases of absolute intolerance to all the arsphenamines.

Bismuth preparations serve a particularly useful turn in the treatment of late neurosyphilis in which symptoms overshadow the serologic findings. In the absence of the "red flag" syndrome, and in the presence of pains, paresthesias and degrees of symptomatic disability and emaciation in which, for one reason or another, an arsphenamine is contraindicated, bismuth is superior to insoluble mercury both on the score of absence of complications and positive therapeutic effects.

In dealing with the latent case in which, after careful examination, only the necessity for maintaining the *status quo* becomes apparent, bismuth is again distinctly superior to mercury on the score of greater effectiveness and lower toxicity.

The weaknesses of bismuth have already been sufficiently mentioned. The tendency to trust too much to it on account of its spirillicidal and healing power is a very serious matter in modern practice and justifies sharp criticism of some of its proponents, particularly among manufacturers of pharmaceuticals. Under no circumstances should bismuth ever be used alone, that is, without an arsphenamine, in the treatment of early syphilis. In the treatment of syphilis of the liver and heart, the question of induced therapeutic paradox even when bismuth is used alone remains to be settled. Under even the best circumstances it must be admitted that bismuth is as yet an unevaluated drug.¹⁰¹ Its very apparent merits, during the first decade of its use, may, though in all probability they will not, be displaced by proof of serious shortcomings. As the matter stands today, the advanced syphilotherapeutist tends to speak of mercury almost as of a forgotten drug.

Certain technical considerations involved in the use of bismuth salts and a discussion of bismuth reactions follow.

Mercury in the Treatment of Syphilis.—The gradual supplanting of mercury by bismuth has had two not altogether undesirable effects. It has increased the controllability of the disease by keeping the patient more closely under the observation of his physician, and it has done away with a method of low efficiency, namely, mouth administration, and a messy and unsatisfactory, though very effective, type of treatment, the mercurial inunction. In this impending exit of oral therapy and rubs, the writer hopes to see the mercurial to which Hutchinson first gave his allegiance, namely, mercury, with chalk, retained. This preparation, the least irritating and one of the most effective for mouth medication, can hold a limited field of usefulness in the benign syphilis of elderly persons. The dose ranged from 1 Gr. (0.065 Gm.) three times a day, to 3 Gr. (0.195 Gm.) three times a day. In pronouncing the formal ritual of damnation on the use of mercury given by mouth in the treatment of early syphilis, it is a great relief to the modern syphilologist to be able to

offer as a substitute something like bismuth intramuscularly administered, which can be employed with a degree of comfort to the patient and absence of reaction almost comparable to that which made the popularity of the protiodide pill. The mercurial inunction, while still a useful method of treatment for hospital practice, will, the writer believes, inevitably be supplanted by bismuth intramuscularly.

Certain points about the mercurial inunction should be consistently borne in mind by its users. It is the slowest in action of all the available heavy metal preparations of really significant therapeutic effectiveness. With the ordinary dosage of 4 Gm. (60 Gr.) of a 50 per cent ointment, the patient does not reach saturation with the metal until at least two weeks have elapsed, and a therapeutic test with inunctions or inunction used as preparation for subsequent arsphenamine treatment cannot be accomplished in a shorter period than six weeks. This leisurely quality is mainly useful in hospital cases and in dealing with hepatic and cardiovascular syphilis, when even the slightest suggestion of therapeutic shock or paradox must be avoided. The mercurial inunction probably gives rise to more stomatitis and cutaneous irritation than any other one form of treatment for syphilis. This makes it, at least on the latter score, particularly unfit for use in conjunction with intensive arsphenamine therapy and makes its replacement by bismuth in the management of early syphilis especially welcome. Mercury administered intramuscularly is distinctly inferior in therapeutic value to the corresponding use of bismuth, though there can be no question that mercurial preparations are susceptible of pharmaceutical improvement to the point where they at least more nearly compare to those now easily available in the bismuth field. The advent of bismuth will in all probability completely displace the use of metallic mercury as such, either in the gray oil or in supposed colloidal suspension. The one preparation of mercury which still holds an undisputed place, in the writer's experience, is the **soluble mercurial salt** and particularly the succinimide. The action of a soluble mercurial is absolutely free from therapeutic shock or paradox and yet is remarkably rapid. In fact, $\frac{1}{4}$ Gr. (0.016 Gm.) doses of mercury succinimide, given intramuscularly five days a week, are almost the equal of the most rapidly spirillicidal bismuth salt, though the action upon the general defense mechanism is probably very much more pronounced. This makes the soluble mercurial salts excellent for the quick preparation of acute neurosyphilis and for use in place of bismuth in critical situations involving the heart and aorta and the liver. Its value in contributing to the restoration of compensation in syphilitic hearts can be demonstrated.¹⁰² It has, moreover, a very considerable degree of nonspecific effect upon such conditions as choroiditis. The author therefore believes that there is a very useful field for mercury succinimide in aqueous or glucose solution with or without a small amount of local anesthetic such as butyn or butyl alcohol. The drug, like all soluble heavy metal preparations, must be given several times a week; and a series of 20 to 30 injections of $\frac{1}{4}$ to $\frac{1}{2}$ Gr. (0.01–0.016 Gm.) each from three to five times weekly makes a very satisfactory course. Occasionally patients are intolerant of soluble mercurial salts and may develop a severe diarrhea or marked renal irritation. This, however, can usually be avoided by proper attention to the prevention of complications from heavy metal treatment as subsequently described.

Relative Worth of Bismuth and Mercury.—In theory it is desirable to retain mercurial therapy to the extent of at least one-third the total amount of heavy metal used in any given case in order to provide against the contingencies incident upon the unevaluated qualities of bismuth. The question as to which is the better drug cannot be regarded as even approaching a conclusive answer from the standpoint of the treatment of syphilis as such. So many complicating factors enter into the situation—including the selection of drugs, the frequency of administration, the vehicles employed, etc.—that it is impossible to make authoritative pronouncements. In a recent study of relapse in syphilis undertaken by a group of cooperating clinics it was decided, on account of the obvious complexity of the problem, that no emphasis should be given to the rather striking figures on this matter which were disclosed by the investigation. It was found that relapse occurred in only 3.6 per cent of a large series of patients receiving arsphenamine and bismuth for the treatment of early syphilis, as compared with 9.6 per cent of those who had received arsphenamine and mercury.¹⁰³

It may be said, then, that the best practice still countenances and in fact insists upon the use of both drugs, if for no other reason than because a number of evidences exist for the belief that syphilis responds better to a multiple therapeutic attack than to the over-consistent use of any one drug.

The Iodides.—Iodides have lost popularity in recent years because a good deal of their healing action has been taken over by the arsphenamines and because the trend of modern treatment has been so generally away from mouth medication. The action of iodides in the treatment of syphilis is purely nonspecific. That is, they act by promoting the lysis of granulomas and the prevention or resolution of fibrosis. The inorganic iodides of sodium and potassium are still the most widely used, the cheapest and the most accessible. They answer the large majority of therapeutic purposes, though one occasionally meets a case of marked intolerance which is better served by the use of such preparations as siomine and lipiodine. There is a distinct difference in the pharmacologic behavior of sodium and potassium iodide, as studied by Osborne,¹⁰⁴ but there is no evidence on the clinical side which the writer has been able to detect that there is any real difference between the two drugs. Certainly the toxic action upon the heart from the potassium ion is not clinically apparent, and, if anything, potassium iodide would seem to be slightly more effective because of the larger amount of iodine protein detectable in the blood serum after its administration as compared with the use of the sodium salt. Large doses have some distinct advantages and are quite needlessly feared by the majority of practitioners. The concentration of the drug in the nervous system can be maintained at a fairly high level by doses of the potassium salt ranging from 50 to 150 Gr. (3.33 to 10 Gm.) three times daily. On the other hand, a long experience and the experimental observations of Pearce¹⁰⁵ have tended to show that there are good effects upon the general well-being of persons and animals infected with syphilis through the use over a period of months and even years of very small doses, such as 5 Gr. (0.33 Gm.) three times a day. The tendency to reaction seems at times to be less with the larger doses than with the smaller ones.

With respect to the intravenous use of iodides, only the **sodium** salt is recommended. The dose should be large, for the principal advantage

to be gained by the intravenous administration of this drug is a temporary very high concentration in the nervous system. As Osborne has shown, there is no object in administering less than 10 Gm. (150 Gr.) of sodium iodide in 10 per cent aqueous solution every day or every other day, for the administration of 100 Gr. (6.66 Gm.) of potassium iodide three times a day by mouth maintains a concentration of iodine in the cerebrospinal fluid equal to that of a smaller dosage of sodium iodide intravenously. There is no object in giving iodide intravenously in cardiovascular syphilis if it can be tolerated satisfactorily by mouth. In the administration of iodide by mouth the following principles are useful. It should be given in aqueous solution, not in milk, the dilution being at the rate of 50 Gr. (3.33 Gm.) to each eight ounces of water ingested. To give the drug after meals simply retains it in the stomach with irritative effect. All **intravenous use** of the drug **should be preceded by at least two days of oral administration** of 20 Gr. (1.33 Gm.) three times a day. Where really huge doses must be employed, the entire day's quantity can be put in a gallon or more of water and the patient induced to drink it in lieu of other fluids throughout the 24 hours.

FEVER AND OTHER NONSPECIFIC METHODS IN THE TREATMENT OF SYPHILIS

The large item of nonspecific effect entering into all aspects of the treatment of syphilis cannot be better exemplified than by the rising importance of such procedures as fever therapy in the management of the most refractory complications of the disease. Attention has particularly been drawn to this field by reports of the good effect of milk injections in the treatment of interstitial keratitis and by the remarkable accomplishments of Wagner von Jauregg¹⁰⁶ in the **malarial therapy** of paresis. The mode of action of these forms of treatment is not clearly understood. It has been contended that the entire effect of fever therapy is due to the action of a foreign protein used to produce the fever, whether in the form of a living or a killed micro-organism. It has also been contended that the chill which precedes the rise of temperature is an important influence in the production of the effect. Both these contentions seem to have lost ground under the demonstration by Schamberg¹⁰⁷ that simply raising the body temperature of experimental animals by hot baths is capable of very materially affecting the course of the disease through the unfavorable growth conditions for the *Spirochaeta pallida* induced by the rise of temperature. The most recent demonstration by Neymann and Osborne⁸² of the excellent therapeutic effect on paresis of rises in temperature induced by **diathermy** without the use of any foreign protein seems quite conclusively to establish the merit of fever, as such. Such evidence, provided it is shown that the effects of diathermy are as lasting as those of induced infection, will probably lead to the retirement from the field of typhoid-paratyphoid vaccine, and of malaria, rat-bite fever, relapsing fever, and similar agencies involving the use of living or dead parasites.

The utilization of **milk**, **intramuscularly** injected, for assistance in reversing refractory positive serologic tests and in treating refractory cases of interstitial keratitis is comparatively simple. From 2 to 10 cc. of an ordinary grade of clean, marketable milk, including all constituents and boiled for five minutes, are satisfactory. Occasionally anaphylactic reactions occur and resemble the nitritoid crises and acute

anaphylactic outbreaks following the administration of arsphenamine. **Adrenalin and atropine should therefore always be in readiness.** The injections may be given once or twice weekly deep into the buttock, and care must be taken that the milk is not introduced directly into the circulation. Malaise and a certain amount of general systemic reaction, sometimes accompanied by fever, occur following each injection. A good deal of the effect may be due to bacteria in the milk.

Typhoid-paratyphoid vaccine can be used for the production of fever, as described by Kunde, Hall and Gerty,¹⁰⁸ and by Kemp and Stokes. The disadvantage of the method lies in the rapid acquisition of immunity to the micro-organisms resulting in poor temperature response. The suspension should be given intravenously, the initial dose being 200 million organisms and this being rapidly increased through a range as high as 4,400,000,000 by the twelfth dose. A chill within half an hour is followed by a rapid and marked rise in temperature which subsides after from four to eight hours. Nelson has proposed a method of securing higher temperatures with typhoid vaccine, by giving a second injection at the height of the fever.¹⁰⁹ **Neosaprovitan** is an example of a preparation containing saprophytic bacteria which is destroyed in the blood stream with a rise of temperature. Sodium nucleinate has also been employed for the same purpose in the earlier experimental studies but is now practically given up. One of the most recent methods for the induction of high temperature consists in the intramuscular suspension of **finely divided sulphur in oil.** This method,¹¹⁰ as discussed before the Congress on Dermatology and Syphilology in Copenhagen (August, 1930), is handicapped by the very severe pain which it induces, which must be controlled by morphine. The rise in temperature, however, is very marked, the therapeutic effect good and the mortality and morbidity said to be practically negligible.

Of all the methods now available for the induction of therapeutic effects by fever, the most popular is that of infecting the patient with **tertian malaria.** In the treatment of general paresis, which is its major field, the use of therapeutic malaria has led to approximately 33 per cent of restoration of patients to complete mental and physical health, 33 per cent of improvements without restoration to economic status, and 33 per cent of failures. The mortality, depending on the method of selection of patients and the experience and caution of the therapist, has ranged from 1 to 30 per cent, with the majority of reports ranging between 5 and 10 per cent. There can, therefore, be no escaping the fact that malarial therapy in average hands has the highest mortality of any single mode of procedure in the treatment of syphilis at the present day. This places it definitely among last instead of first resorts, makes it a method to be used by experts, and limits the justification for its use to those patients who have unmistakable warnings of critical complications involving the nervous system. There can be no escaping the fact that fever therapy, and malarial therapy in particular, has been much abused and has been applied without discrimination to a wide range of cases. None the less, this fact does not detract from the importance and success of the method where properly controlled and applied. The one most conspicuous contra-indication to fever therapy is cardiovascular disease, and this, from its very nature, is estimated only with difficulty in the average patient of middle life and beyond. For this reason the writer has been disposed to set 45 years of age in the syphilitic subject

as an empirical age limit beyond which the adoption of fever therapy becomes potentially dangerous and to be undertaken only with exaggerated precaution and much misgiving. A number of instances in which his objections were overruled with disastrous results have seemed to support the author's contention. The necessity for very critical and conservative judgment in the selection of patients, the necessity for thorough familiarity with complications, particularly the fall in blood pressure and rise in blood urea which are particularly serious warnings of danger, and the rather delayed convalescence and tendency to stormy cerebral episodes, furunculosis and so forth, all make the malaria inoculation method one for hospital use only and one only to be undertaken after adequate consultation and by an experienced "malarialist." Notwithstanding these strictures upon its use, malarial therapy has held very properly an extremely important place in the modern management of neurosyphilis. This place, it now seems possible, will be yielded to fever induced by powerful diathermy apparatus as recently described particularly by Neymann and Osborne.

Therapeutic malaria is induced by inoculating the patient with 1 to 2 cc. of the blood of a person with a known strain of active tertian malaria. Very serious complications are capable of following the use of unknown strains picked up at random from malarial patients. An incubation period of four to nine days ensues, terminating in the first chill. Following this, the chills and rises of temperature recur with the regularity of the conventional malarial siege. The effect on different patients varies widely and some are severely shocked while others sustain no more than ordinary discomfort. The good effect is largely proportional to the height of the temperature secured and where this lags, it may occasionally be stimulated by the activation of the process with typhoid vaccine. The number of chills required for a satisfactory therapeutic effect ranges from two or three to a dozen or more and is conditioned a good deal by the patient's tolerance of treatment. The siege is terminated by the **oral administration of 8 Gr. quinine** and the majority of malarial therapists follow this by neoarsphenamine. The patient is allowed to convalesce, and during the period of convalescence tryparsamide therapy may be employed in neurosyphilitic patients. It cannot be too strongly emphasized that the **treatment of a patient by malarial inoculation should not be undertaken by persons of small and occasional experience or outside of centers supplied with every equipment for dealing with emergencies.** The practice of sending a patient to a malarial center for inoculation and then returning him to some distant outpost in the country to be cared for without proper facilities is dangerous.

Diathermy.—Two methods of treatment by electrically induced fever have been described, one involving the placing of the patient in a highly charged field between two electrical oscillators and the other involving the induction of fever by diathermic effects obtained with a high-power machine and very large electrodes covering the greater part of the body surface. Only the latter method has given evidence of its safety and practicability. According to Neymann and Osborne, a machine developed for the production of these effects is capable of delivering 4000 Ma. The patient is placed in bed and the electrodes, a single one to the back and a divided one for the thorax and abdomen, are so placed as to cause the current to pass through the thickest parts of the

body. Great care must be taken, in the application of these electrodes, in order to prevent poor contact and the production of superficial burns, sometimes severe. The rise in temperature occurs at first gradually, and then, after it has reached 104 degrees, there is a very sudden rise which follows even the shutting-off of the current. This latter rise may be critical and must be very carefully watched. Temperatures as high as 106 degrees are obtained without great difficulty. The peak temperature is maintained for a considerable period with a gradual decline which adds to its therapeutic effect. The patient should remain in bed under hospital control for at least 24 hours. There is little incapacitating after-effect. Sessions are repeated once a week, or at shorter intervals if the tolerance of the patient is good. The therapeutic results thus far reported, while limited in number, indicate that the effectiveness of this treatment under proper control is equal to that of malarial therapy and quite comparable also to that obtained with tryparsamide in neurosyphilis. Tryparsamide may be given at the height of the fever with apparently good effect.

COMPLICATIONS AND CONTRA-INDICATIONS OF THE TREATMENT FOR SYPHILIS

Nothing is more essential for the successful conduct of the modern treatment of syphilis than thorough familiarity with the cause and prevention of complications. In fact, ignorance on this score constitutes the violation of the sixth great principle of modern syphilotherapeutics already discussed, which too often brings patient and physician to their Waterloo in the struggle with the disease. It is impossible in a presentation of this length to discuss in detail each and every difficulty that may arise in the treatment of the patient with syphilis. Emphasis has already been placed upon the importance and prevention of therapeutic shock and therapeutic paradox. Now that the heavy metals have been discussed, some further details as to the technic of so-called "preparation," or preliminary treatment for the prevention of these complications, may be outlined.

Preparatory Treatment.—Early in the course of a syphilitic infection, that is, within the first several weeks, warnings of risk of serious complications may be drawn from a history of severe and violent headaches or of visual or eighth nerve disturbances, particularly tinnitus and dizziness. If any of these symptoms are present, it is wiser to begin the treatment of the patient with **bismuth rather than arsphenamine**, postponing the latter drug until the symptoms are abated or investigation discloses their lack of significance for the disease. Often a spinal fluid examination may be necessary to establish this fact. After from three to six weeks of bismuth therapy, the patient may usually safely be placed upon an arsphenamine. If the symptoms, as, for example, in a fulminating papillitis or neuroretinitis, are actually endangering the patient's vision, much more rapid effect can be secured by the daily injection of $\frac{1}{2}$ to $\frac{1}{4}$ Gr. (0.01–0.016 Gm.) mercuric succinimide, accompanied by daily injections of sodium iodide intravenously following a two-day tolerance test by mouth. This method of preparation is also usable in less pressing complications. It need not usually be continued longer than two to four weeks, following which an arsphenamine may be employed. In the later phases of syphilis, one must be on the **lookout for structural involvements** which suggest that the disease may flare up in

a critical fashion at some vital point in the beginning of vigorous treatment. Thus, for example, while gumma of the larynx is not a particularly serious aspect of the disease from the standpoint of amenability to treatment, death may result from the transiently induced edema following a first injection of an arsphenamine. A patient with extensive nuclear involvement in the brain may be thrown into a sudden and lasting paralysis following the Herxheimer effect produced by a single injudicious arsphenamine injection. Accordingly it is wiser, as a general principle, to place practically all advanced syphilis, especially when it has been impossible to make a thorough-going examination, upon some form of **slower-acting treatment** such as the use of bismuth or a soluble mercurial salt with iodide. The length of the period of preparation for arsphenamine must be determined by the status of the individual case, but 20 injections of from $\frac{1}{4}$ to $\frac{1}{2}$ Gr. (0.01–0.016 Gm.) of **mercuric succinimide**, at the rate of from three to five injections a week, or from four weeks to three months of **inunctions**, or from four to twelve weeks of an insoluble **bismuth salt intramuscularly**, are fairly representative of the ordinary requirements.

Therapeutic paradox in its field of greatest seriousness, namely, syphilis of the heart and liver, is best controlled by the use of the mercurial inunction with iodide, over a period of weeks or months, and even in some cases by the initial administration of mercury and iodide by mouth, to be followed with extreme caution by inunctions and then by bismuth. Fortunately, as has been already indicated, bismuth in very small doses and bismuth arsphenamine sulphonate may be given so as to render other forms of preparation unnecessary. In general, however, it is better to err in late syphilis on the side of excluding the arsphenamines where critical structures are involved than to err in the direction of their premature employment.

Drug Complications as Such.—A grouping within this highly important field for complications may be attempted as follows:

1. *Blunders.* First, the most terrifying and too often the most unpardonable of blunders in the use of the arsphenamines is the administration of concentrated unneutralized arsphenamine in place of neoarsphenamine. Not a year passes that this accident does not occur, often in a well-managed clinic or hospital rather than in the office of the inexperienced practitioner. The prevention of this accident on syphilologic services can be accomplished only by the most unceasing vigilance, and no chief ever feels himself entirely free of an anxiety which some one of his lesser associates or assistants may suddenly and without warning convert into an agonizing reality. Much can be accomplished by training every hospital interne to read labels systematically in advance of the preparation of any drug; by insisting that no package of arsphenamine (usually plainly marked) shall be opened or prepared for opening except in the presence of the operator; and by the thorough drilling-in of the rule that any arsphenamine preparation which does not completely and almost instantly dissolve in 10 cc. of water is to be thrown out. The solubility of "606" in the vast majority of preparations is such that there is at least a very definite retardation, if not an absolute refusal to go into complete solution in this amount of water and this fact should at once arouse suspicion. Only experts can be relied upon to distinguish the two drugs by their color and odor. To prevent the administration of diluted but unneutralized

arsphenamine, which, fortunately, is less dangerous than the administration of concentrated arsphenamine solution, a drop or two of phenolphthalein added to every bulk solution of an arsphenamine, to turn pink on alkanization, is a very useful protection.

2. The second type of blunder concerns the use of improperly prepared distilled water for making up solutions in intravenous work. A chill and a rise in temperature following an injection of an arsphenamine invariably raises two questions: first, was the water absolutely pure. (triple distilled)? and second, was a piece of new tubing, untreated or improperly treated with sodium hydroxide (tubing reaction), used in the administration? A chill and rise in temperature may follow occasionally the use of impure sodium iodide solution and should invariably be the occasion for an overhauling of staff technic.

3. A third group of blunders includes the occurrence of emboli from the improperly controlled injection of insoluble heavy metals into the muscular and subcutaneous tissues. If a vessel has been penetrated by the needle point or the injection mass in its spread ruptures a vessel, the patient is at once either killed by a cerebral embolus or, if the embolus has been pulmonary, is thrown into a violent fit of coughing followed by a rise of temperature and symptoms of a localized lesion. The prevention of embolic accidents is comparatively simple and calls for nothing more than a few seconds' aspiration on the piston of the injecting syringe after the needle attached to the syringe has been introduced into the muscle. It is insufficient simply to detach the syringe from the needle and wait for the appearance of blood.

4. The fourth type of avoidable blunder consists in the production of infections from dirty technic. It is only justice to say, however, that the majority of abscesses following intramuscular injection are not due to infection but are sterile reactions against the drug, usually on account of its imperfect physical division and sometimes because of idiosyncrasy. It should go without saying that only a careful aseptic technic has any place in the modern treatment of syphilis.

GASTRO-INTESTINAL REACTIONS.—The second large group of drug complications as such involves the gastro-intestinal tract. The reactions which troubled our forebears in the field, namely, gastro-intestinal intolerance of irritating mercurials, have now been done away with by the change in practice. Their place has been taken by the gastro-intestinal reactions to the arsphenamines. These include various degrees of nausea, with or without vomiting, diarrhea, and colic. Reaction on the part of the gastro-intestinal tract is based chiefly upon the fact that it is the principal route of elimination for the arsphenamine group of drugs, a larger part leaving the body through the bile and the gastro-intestinal tract than by way of the kidney. Gastro-intestinal reaction to the arsphenamines usually begins at the time that the partition of the arsphenamine molecule into arsenoxide and other decomposition products occurs, namely, at about the fifth hour after injection. On account of the gastro-intestinal route for the elimination of these products, it is especially important that each injection of an arsphenamine be followed within 12 to 18 hours by a **fairly quick-acting cathartic**, of which magnesium citrate (one-half bottle) serves most purposes. A certain amount of control of gastro-intestinal reaction is secured by very slow administration of the drug; another portion is controlled by insisting that the patient receive his injection with the stomach prac-

tically empty. This latter requirement, however, should not be too absolute, for some patients are rendered more instead of less reactive by preliminary starvation. Tea and toast are usually well tolerated two hours before the treatment. It is important also not to eat heavily following injection, and those patients who can exercise the greatest restraint in this particular, short of unnecessary starvation, have the smoothest courses. Any patient who shows a tendency to chronic constipation should, throughout a course of antisyphilitic treatment, be given the assistance of a mild laxative such as rhubarb and cascara, with a little milk of magnesia. It is **dangerous to use drastic catharsis** and it is also undesirable to include an excess of roughage in the diet, for both these measures may occasionally lead to severe bloody diarrhea. During the attack of nausea or vomiting following treatment, great relief can be secured by giving the patient two glasses of warm water and some assistance in emptying an overfilled stomach, following which he is fed cracked ice to be chewed and swallowed and not allowed to melt in the mouth. Half a dram to a dram of baking soda dissolved in a small amount of very cold water is often welcome, and carbonated drinks, including particularly ginger ale poured on ice, are also serviceable. In the prolonged and obstinate vomiting that occasionally appears as an idiosyncrasy to arsphenamine, an injection of adrenalin subcutaneously (10 to 20 minims) and occasionally alcohol by mouth, particularly as beer, may be useful. An ice bag to the pit of the stomach often gives a good deal of symptomatic relief from nausea.

THE MOUTH.—All the drugs used in the treatment of syphilis have a certain amount of effect upon the mouth. Stomatitis is an occasional complication of arsphenamine therapy and when it appears is always of serious significance. A differential count of the leukocytes should be taken immediately. Stomatitis as a symptom accompanying critical and even fatal aplastic anemia was early noted by Moore and Keidel.¹¹¹ A differential blood count to be taken early, with the appearance of a high eosinophilia and many immature forms, is a warning of the seriousness of the situation. The slightest tendency to bleed from the gums with purpuric hemorrhages into the mucosae and the lips is always an alarming symptom of the group of arsphenamine reactions characterized by hemorrhagic purpuras and, like stomatitis, associated usually with evidence of acute aplastic anemia. Further details are given under Vascular Injuries. Both mercury and bismuth are responsible for stomatitis and in both cases the frequent appearance of stomatitis may be regarded as evidence of inadequate or unskilful management. Occasionally, however, stomatitis does appear even on the best regulated services, as an epidemic episode apparently associated with the general prevalence of throat and mouth infection. The appearance of stomatitis is not to be used as a clinical guide to satisfactory saturation with the drug responsible. The very great importance of avoiding heavy metal stomatitis makes it a first principle that all patients under treatment should have suitable dental prophylaxis applied at the earliest possible time, with removal of infected teeth and the cleaning up of pockets and repair of dental caries. The second item contributing to a healthy mouth under heavy metal treatment is an alkaline and mildly astringent cleansing agent. One of the most satisfactory of these is the potassium chlorate, oil of peppermint and chalk toothpaste devised by Unna and widely used throughout the world. While objected to by

some dentists as too alkaline for ordinary purposes, there can be no doubt of its value as an alkalinizing and oxidizing agent in protecting the mouth against the saprophytic organisms which are important agents in the production of mercurial and bismuth stomatitis. Occasional washing of the mouth with dilute hydrogen peroxide solution, and the painting on the gums of a mixture of one part tincture kino and two parts tincture myrrh are very useful (Wile). In the use of mercury, which is probably more injurious to the mouth than bismuth, it is also important to insist upon an **acid-free diet**, for even so minor an indiscretion as the eating of a single sour apple has, in the writer's observation, precipitated an attack of mercurial stomatitis. Bismuth stomatitis fortunately presents a warning in the form of a pigmentary line at the junction of the gums and teeth, with occasional pigmentation of the buccal mucosae. An even earlier sign of bismuth overdosage with respect to the mouth, as pointed out by Klauder, is an extraordinarily heavy fetor to the breath. Both these signs, while not necessarily indications for the cessation of treatment, are warnings that a most vigorous prophylaxis is essential. It appears that the simultaneous use of an arsenical with bismuth has distinctly a prophylactic effect upon mouth complications, possibly because of its influence on the spirochetal flora, including especially Vincent organisms in the mouth.

SPECIAL SENSE ORGANS.—The important symptoms from the special sense organs (eye and ear) have already been mentioned in connection with therapeutic shock. Ivan Lillie¹¹² has emphasized the importance to subsequent treatment decisions of an examination of the eyes of every patient with syphilis, including fundus, perimetric fields and visual acuity before he receives the first injection of an arsphenamine. In the author's opinion it is inadvisable to give an arsphenamine preparation to persons showing definite evidence of primary optic atrophy; this in addition to the necessary preparation of all patients with papillitis and neuroretinitis.

VASCULAR INJURY.—The commonest and fortunately the least harmful of the vascular injuries produced in the course of antisyphilitic treatment is the nitritoid crisis following the administration of an arsphenamine. This reaction usually begins after the injection has been partly given and is often a sign of too rapid administration of the drug. A choking sensation, cough, gasping, edema, and intense flushing of the face, with loss of consciousness if the injection is continued, are the symptoms. All patients should be watched throughout the time they are receiving an injection, and if this reaction appears, the injection must be stopped. **Epinephrine solution**, 1 to 1000, 10 to 20 minims according to severity, should be given subcutaneously. The epinephrine solution should be always at hand. Patients who react repeatedly in this way may be given atropine hypodermically, 1/50 to 1/75 Gr. (0.0013 to 0.00086 Gm.) 20 minutes before injection, and the dose of the arsphenamine may be split in two parts, the first tenth being given 20 to 30 minutes before the remaining nine-tenths. Delayed nitritoid reactions have been described as occurring following intramuscular injection of sulpharsphenamine and bismuth arsphenamine sulphonate. In these cases the divided-dose technic and the use of atropine as a preparation will control the situation. In some cases there is evidence that the tendency to this type of reaction wears off, after a time, of itself. Nitritoid and gastro-intestinal reactions to arsphenamine sometimes stand

in close relation and the appearance of nitritoid reaction is very apt to be followed by an increasing degree of severity in gastro-intestinal reaction.¹¹³ Nitritoid reactions, while intrinsically not serious, should in general be taken as a warning to proceed cautiously and with a careful eye to the state of the vascular system during subsequent treatment. The best current explanation of the process is that it is due to intra-vascular agglutination of red blood cells with multiple pulmonary emboli.¹¹⁴ At times the termination of a nitritoid crisis in an outbreak of urticaria suggests the possibility of anaphylactic origin.

The two gravest and, in fact, almost invariably fatal accidents of arsphenamine administration are *hemorrhagic encephalitis* and *aleukemia haemorrhagica*. While, fortunately, comparatively rare, they are common enough so that they may be expected to appear in an average large practice in this field at any time. *Hemorrhagic encephalitis* is due to an edema of the brain associated with multiple miliary hemorrhages. Like aleukemia haemorrhagica, it occurs usually only in conjunction with the administration of a sulphoxalate arsphenamine (neoarsphenamine, sulpharsphenamine, bismuth arsphenamine sulphonate). The earliest symptom is mental confusion, rapidly passing into coma or muttering delirium, not infrequently accompanied or even preceded by severe convulsions. This may be confused with a cerebral therapeutic shock, but can be differentiated from it by the usual marked response, in hemorrhagic encephalitis, to large doses of epinephrine administered subcutaneously or even intravenously. There have been reported recoveries from hemorrhagic encephalitis, practically always as a result of early, intensive and prolonged administration of epinephrine. The administration of hypertonic saline solution intravenously, together with lumbar puncture, can be tried on the basis of a resemblance to the "wet brain" of delirium tremens. *Hemorrhagic purpura* with aplastic anemia (aleukemia haemorrhagica) is one of the most terrifying and fatal of complications. Not infrequently there will be some warning that it impends, in the form of slight bleeding and spotting of the mucous membranes of the mouth, or the appearance of a few petechiae about the wrists and ankles after a preceding injection. It is for this reason that it is of vital importance to inquire into such a complication at each injection of the drug. At times the onset is fulminating; bleeding from the mouth, large petechial hemorrhages into the skin, subperiosteal suggillation and melena combining to produce a rapid fall in hemoglobin and red count with the gravest prostration. The blood picture is not always characteristic at the outset, the fall in platelet count and absence or great decrease in leukocytes not appearing until some time after the hemorrhages begin. In those cases associated with stomatitis, the drop in leukocytes may begin at once. The condition is practically untreatable in its acute or progressive phase and while coagulants, blood transfusion and so forth have been tried, the arrest of the process, if arrest occurs, seems to be a matter of uncontrollable circumstance. Once the hemorrhages stop, every possible effort should be made to restore the functional power of the bone marrow by the technic of Minot. With the use of **large doses of the pernicious anemia fraction of liver extract, a diet rich in meat, the administration of cod liver oil and viosterol and judiciously administered transfusion**, the patient may be tided over to a recovery. As in agranulocytosis, necroses of the most serious and extensive character may appear in the mouth, associated, in all probability, with the

drop in resistance to saprophytes incident upon the depletion of the leukocytic defense. The mortality of this complication, while not definitely known, can hardly be less than 50 to 60 per cent.

RENAL INJURIES.—Nephrosis and nephritis are important complications of all forms of treatment for syphilis.¹¹⁵ In general, the kidney tolerates arsphenamine best, bismuth next and mercury least. The iodides are practically without irritative effects. Accordingly, in the treatment of patients who are already nephritic, it may be expected that the drugs will be tolerated in the order named. Chronic nephritis is sometimes very much more tolerant of the arsphenamines than of the heavy metals and even makes a good showing with bismuth. There is a distinct type of treatment nephrosis occurring in intensively treated cases, particularly of early syphilis, with a very high albuminuria, many casts, lipid crystals in the urine and occasionally traces of blood. This nephrosis usually ends in recovery spontaneously within six months to a year after the cessation of treatment. The urinary picture presented is quite different from that of the conventional renal irritative effects of the heavy metals, particularly mercury. In the urine of renal irritation due to mercury, the first abnormal sign is polyuria. The second is the appearance of hyaline and granular casts, the third is a slight or moderate increase in albumin and the fourth is the appearance of blood. It is quite inexcusable ever to push renal irritation under treatment to the point of hematuria. Renal irritation from mercury and bismuth (this latter comparatively rare) must be distinguished from acute syphilitic nephritis by the fact that in acute syphilitic nephritis the quantities of albumin exceed those found in almost any other type of nephritis, the urine almost boiling solid, as in the case of eclampsia. Casts and blood cells are present in large amounts.

Renal injury can be forestalled by the periodic examination of the urine throughout the course of treatment, once each week if the patient is under mercurial therapy, and once in two weeks if the patient is under either arsphenamine or bismuth. It is surprising how much treatment the kidney will tolerate without permanent ill effect and, since the advent of bismuth, without any signs of irritation. In general, the **cessation of treatment** for a short time, and particularly of treatment with mercury, is all that is necessary to restore normal conditions. Alkalinization, while formerly much used, and the low-protein, salt-free diet are now needed only in occasional cases.

HEPATIC INJURIES.—The liver is the major storage depot for the arsphenamines in the body and likewise sustains irritative effects from both mercury and bismuth. Fortunately, its margin of tolerance is very large, although there is some evidence to indicate that chronic hepatitis is becoming a treatment complication of a considerable proportion of patients with syphilis,¹¹⁶ usually in a subthreshold degree. By no means all of the jaundice and hepatic enlargement observed in patients under treatment for syphilis is to be ascribed to arsenical injury of the liver, though the *post hoc* tendency of much of our thinking makes it difficult for the clinician to escape the temptation to ascribe all jaundice in the course of treated cases to the arsenical element. Syphilis itself is responsible for at least six different types of liver involvement to be mentioned under Syphilis of the Liver and Spleen, certain of them affecting as high as 10 per cent of patients in the latent phase of the disease. Hepatic injuries from treatment, in addition to the arsenical type, in-

clude Herzheimer or therapeutic shock effects on patients, both early and late, with active hepatic syphilis, therapeutic paradoxical effects on patients with extensive diffuse or miliary gummatous hepatitis, in which, though no acute reaction occurs, late decompensations with injuries prove very serious; and increased general and perhaps especially cutaneous reactivity due to lessened storage capacity in a badly involved syphilitic liver. An important and, the writer believes, frequently overlooked factor in hepatic injury in the course of treatment for syphilis is the purely extraneous one of intercurrent infection responsible for catarrhal jaundice, often secondary to duodenitis; and intercurrent infectious influences acting below the threshold of recognition in predisposing toward fulminating accidents, such as acute yellow atrophy, in which the arsenical effect may be conceived as superimposed upon damage due to other causes.

The practical attack on the problem of hepatic injury in treatment for syphilis should, it seems, take the following directions. Any sign of involvement of the liver, usually as evidenced by enlargement but also by traces of jaundice and a history suggesting gallbladder disease, should be carefully noted in advance of any form of treatment. Especially if the case is an early one, bismuth preparation at least should be employed before an arsphenamine is considered. An acute increase in the size of the liver with tenderness and accentuation or appearance of jaundice immediately following the first two or three treatments, even with very small doses of an arsphenamine, is indicative of a therapeutic shock type of reaction. In the later cases where therapeutic paradox is to be avoided, the safest plan consists in the prolonged preparation of the patient or even his exclusive treatment with mercury and iodide. Several months of inunction often constitute the safest procedure, preferable even to bismuth. Assistance must be had in differentiating the very rare cases of acute yellow atrophy due to syphilis from those which occur in the course of antisymphilitic treatment, for the outlook in syphilitic yellow atrophy (*icterus gravis*) is absolutely dependent upon intensive treatment, while a continuance of intensive treatment may be fatal to the other types. Milian and other French observers have insisted that many cases of acute yellow atrophy which have been observed at times in the intervals between courses of treatment, instead of being late toxic effects of the treatment itself, are in reality fulminating hepato-recurrences due to localized revival of the infection in the liver, much as in the case of neurorecurrence in the nervous system. In these cases, if they can be identified, intensive treatment for syphilis is the only life-saving measure. The catarrhal infectious type of jaundice¹¹⁷ may occur either during a course of treatment or at periods varying from weeks to years after its termination. The severity of the process may range all the way from slight yellowing of the sclerae with slight abdominal discomfort and anorexia passing off in the course of two or three weeks to a rapid onset of jaundice, hepatic enlargement, abdominal pain, subsequent shrinkage of the liver and death from acute yellow atrophy. Severe cases of this type tend to be accompanied by other manifestations of severe arsenical injury, including polyneuritis and dermatitis. In both types of cases the stools may or may not be acholic and the urine invariably contains considerable amounts of bile. On account of the difficulty in differentiating catarrhal infections from arsenical jaundice, it is usually wisest to **discontinue treatment tem-**

porarily, to administer **sodium thiosulphate** in 0.5 to 1 Gm. (7.5–15 Gr.) doses on alternate days for perhaps three injections, to give **glucose intravenously** in considerable amounts, and to **put the patient to bed**. Wilhelm¹¹⁸ called attention to the great relief in the catarrhal cases which often follows duodenal drainage and magnesium sulphate lavage. The risk of confusion with acute septic cholangitis must be borne in mind, for surgical intervention in these cases of catarrhal infectious jaundice accompanying treatment for syphilis has a high mortality and should by all means be avoided. As a rule a patient with catarrhal jaundice is much less ill than one with septic cholangitis; there is little or no fever; there is a disproportionate prodromal gastrointestinal phase, and sodium phosphate catharsis with rest in bed and duodenal lavage produces very prompt response. In those cases which are seen as they develop an acute yellow atrophy, only general detoxifying measures are of any avail. It seems probable that outbreaks of epidemic infectious jaundice may be responsible for some of the singular discrepancies between the experience of different services in various parts of the country in successive years with reference to the incidence of jaundice in their use of the arsphenamines.

CUTANEOUS INJURIES.—These are disconcertingly common and are produced in some degree by all of the drugs used in the treatment of syphilis, the most important group being that ascribed to the arsenicals. The heavy metals, and mercury in particular, may in susceptible persons give rise to erythemas, usually transient and ceasing upon the discontinuance of the drug. A more serious type of reaction is the spreading, patchy dermatitis which particularly tends to follow the use of mercurial inunctions and which is a general reaction to a local form of irritation. It appears first about the flexures and folds of the skin, especially following too vigorous rubbing of the ointment into a hairy surface, and may, by extension, pass over into a complete case of exfoliative dermatitis, though such a consummation is rare. Both mercury and bismuth, and in fact almost any toxic substance administered intramuscularly, may produce a sudden outburst of dermatitis, beginning usually about the face and flexures and rapidly covering the entire body with the typical picture of exfoliative dermatitis. These complications of heavy metal treatment may be indistinguishable from arsenical dermatitis but usually occur in patients who have had both types of drug. Patients who have had an exfoliative dermatitis due to an arsphenamine should not be placed on intramuscular heavy metal medication without previous patch tests for heavy metal sensitivity, and without considerable caution in dosage, for a premature resort to intramuscular heavy metal medication may revive an arsenical dermatitis. Secondary infection with impetiginous and furuncular eruptions may complicate all forms of cutaneous reaction to antisymphilitic treatment, including heavy metals. Inasmuch as bismuth is much less likely to cause cutaneous reactions than mercury, it is the drug of choice where a discrimination must be made on this score.

The iodides give rise to the familiar iodide acne, to the less familiar vegetative eruptions (iodide buttons) and to the very severe and sometimes fatal bullous erythema multiforme or toxic erythema and generalized dermatitis of acute iodide poisoning. The patient who easily develops an iodide acne is usually the person with a seborrheic tendency and a background of ordinary acne manifestations, who can

be materially benefited by sharply reducing the intake of carbohydrates in his diet and by the use of a simple sulphur-containing lotion, such as *lotio alba*. The more serious vegetative reaction to iodides can usually be dealt with only by suspending the use of the drug and employing wet dressings and irradiation with small doses of unfiltered x-ray. Protection against bullous iodism can be secured only by testing the tolerance of all patients who are to receive iodine by small initial doses given orally. Since this reaction is very rare but quite unforgettable, the patient is very apt to give a history of it, if inquiry is made. Iodine painted on the skin may be extremely dangerous in patients on the verge of cutaneous reaction to either the heavy metals or arsenic, and for that reason caution must be exercised in its use for disinfecting purposes at the sites of venipunctures and so forth.

Cutaneous reactions to the arsphenamines, even in mild form, occur no oftener than once in a thousand injections under skilled management but are probably somewhat more frequent under average conditions. The reactions include pruritus, urticaria, toxic erythema of macular, papular, morbilliform and scarlatiniform types, fixed exanthems, arsenical lesions, including pigmentation and keratoses; lichenoid eruptions resembling *lichen planus*; exfoliative dermatitis; and herpes. Pruritus without eruption, coming on within a few hours to a day or two after an arsphenamine injection, can occur alone or be part of the prodrome of exfoliative dermatitis. Urticaria usually appears within a few minutes to a few hours after an arsphenamine injection and may be accompanied by asthma-like symptoms or be the sequel of a nitritoid crisis. The response to epinephrine is usually prompt, and ephedrine may be used as a preventive. The toxic reactions, so-called, are relatively acute, suggesting the onset of an acute exanthem, with chill and fever following the injection at an interval of 24 hours or less. From about the second to the fourth day the eruption appears and may be indistinguishable from that of measles or even a rather coarse type of scarlet fever eruption. Edema of the eyelids often occurs but there is no coryza. The comparatively smaller degree of involvement of the mucous membranes, without Koplik spots and with more of a stomatitis in the arsenical complications, assists in differentiation. The fixed exanthems are comparatively rare and consist in the periodic lighting up, following each arsphenamine injection, of a plaque or patch, often on the extremities, which takes on during the acute phase an urticarial character and between injections an appearance suggestive of *lichen simplex chronicus* or dry hyperpigmented eczema. True arsenical lesions, including marked hyperpigmentation, especially of the trunk, with lighter mottling, and hard, sand-grain keratoses of the palms, sometimes with marked thickening, may occur after considerable treatment with the arsphenamines but are rare. While pigmentation following silver arsphenamine, both of the arsenical and the argyrie type, has occurred, it is an excessively rare and practically negligible complication. The lichen planus-like eruptions are of comparatively recent recognition and are sometimes distinguished with the greatest difficulty from recurrent secondary syphilis and from *lichen planus* itself. Herpes, especially of a zosteriform type, may occur in conjunction with arsphenamine intoxication, as with other forms of arsenical poisoning.

The really critical cutaneous complication of arsphenamine therapy is postarsphenamine exfoliative dermatitis. Usually after a prodromal

warning of pruritus which occurs as long as a week or two before the actual appearance of the eruption and has a tendency to produce slight edema of the face and small, red, stippled papules about the flexures, the outbreak of exfoliative dermatitis becomes acute and serious from the outset. The face swells, a marked erythema with early vesiculation and edema appears about the eyelids, wrists, ankles and flexures, and from these sites rapidly involves the entire body. Confluence and oozing set in, the nervous irritability of the patient rises very markedly, and there may or may not be fever. In the very severe cases with early fatal termination, the irritative phase is followed by a profound intoxication, in which jaundice may appear as evidence of involvement of the liver and polyneuritis as evidence of toxic effects on the nervous system. The majority of patients, however, pass into a chronic generalized dermatitis which runs a course of weeks or even months when untreated and often in spite of the best treatment. The more nearly universal the dermatitis, the more marked the oozing and edema; and the more pronounced the lividity or purplish tinge of the skin, the more serious the prognosis and the more prolonged the course. Patchy cases of dermatitis are known to occur following arsphenamine as an arsenical complication, and in such cases treatment with an arsphenamine may even be resumed in case of necessity without very serious results except for the prolongation of the trouble. On the other hand, the acute, edematous cases suggest an allergic background and continuance of arsenical therapy under such circumstances is a risk that no one would wish to assume. As the exfoliative dermatitis progresses the patient, usually profoundly ill, is confined to bed, becomes markedly emaciated, suffers at times from severe and intractable diarrhea and often from the effect of secondary pyogenic infection. This last item may be extremely important and occasional cases seem even to terminate in septicemia. While the edema of the skin subsides and the itching, at first intense, becomes less severe, the scaling on an erythematous base and the acquisition of scratching habits prolong the process and complicate the entire course. A rather pronounced symptom of early and unfavorable prognostic significance, at least for duration, is the severe chilling on exposure of the body even in a warm room. Fever, while present in some cases, is absent in others and is at times associated with what seem to be bouts of secondary systemic infection, particularly exacerbations of tracheo-bronchitis. The sequence of events above described is fortunately, in the majority of cases which survive the first two weeks, followed by a convalescence in which itching slowly diminishes, sweating, which has been suspended, reappears, the lost weight is regained, and the patient finally masters his intercurrent infection. Hyperirritability of the skin and occasional patchy dermatitis may, however, persist for long periods. **The resumption of arsphenamine treatment in individuals who are genuinely sensitive to the drug is followed by an immediate and sometimes fatal relapse.** Hyperpigmentation following all arsenical accidents of this type may be pronounced, but the patient may be assured that they will ultimately clear up.

The treatment of exfoliative dermatitis should be, in the main, preventive and is discussed in the following section under the head of General Detoxifying Measures. Once the onset of an attack is definitely threatened, **sodium thiosulphate** should be given intravenously in doses of 0.5 Gm. (7.5 Gr.), 0.75 Gm. (11.25 Gr.) and 1 Gm. (15 Gr.), the in-

jections being given every other day. At this point in the large majority of cases the writer's experience indicates that this type of treatment should be stopped. It has been observed more than once that its continuance beyond this point seems to increase rather than diminish the severity of the attack. **Glucose solution**, 10 cc. of 50 per cent strength, given intravenously on 2 or 3 successive days, has been very favorably mentioned to the writer by Shaffer. The bowels should be kept open by **saline enemas** but care must be taken not to start a diarrhea which may be difficult to stop. Confinement to bed in a warm room, adequate nursing, close attention to nutrition, a careful check by differential blood count of the possibility of aplastic anemia, and detection of nephritis, if present, are all essential. The local treatment of the dermatitis assumes great importance and is, in the main, best carried out by the use of the **buffered** or **colloid bath**. This may be prepared by the use of either oatmeal and baking soda or of ordinary cornstarch or laundry starch, according to the comfort and individuality of the case. If oatmeal is used, an ordinary thick oatmeal porridge is prepared and placed in a cheesecloth bag which is tightly closed; then the soft, mucilaginous content is washed out by agitating the filled bag in a tubful of water at a temperature of perhaps 87 to 95 degrees, depending on the tolerance of the patient. After the gruel is washed out, the bag may be used for cleansing purposes and baking soda ranging in amounts from one-half to one cupful may be added to the tub of water. Special nursing and bath technic are required for very debilitated patients. The temperature should be regulated by thermometer, should not be so high as to induce prostration; and the patient should be under constant supervision while in the bath. Immediately upon emerging from the bath the skin should be dried by patting rather than rubbing (the excess scale having been removed while in the water). It is then absolutely essential to apply immediately an oily emollient, usually nonmedicated, for which purpose equal parts of olive oil and lime water are fairly satisfactory, or a cold cream containing perhaps small amounts of lanolin, though this latter is apt to be too sticky. The bath may be given from one to three or four times a day, depending on the patient's tolerance and comfort, the last occasion being perhaps an hour before bedtime. The patient may remain in the bath for ten minutes to half an hour or more, care being taken not to produce exhaustion. The diet should be light, those cases suspected of arsenical hepatitis should not receive fats and those patients in whom the seborrheic or oily skin factor seems the more pronounced should have, instead, a reduction of carbohydrates. Exposure to the quartz lamp, as the patient is recovering, small doses of unfiltered x-ray at the hands of experts, careful attention to local pyogenic infections, are all of much importance in various cases. Nurses caring for dermatitis patients should wear rubber gloves of elbow length in giving the bath. Any attempt to tamper with the patient's focal infections (teeth, tonsils, sinuses, etc.) during the course of the treatment for dermatitis may have a serious if not fatal result.

A number of weeks after recovery from the attack of dermatitis, the patient should be carefully tested for sensitivity by the patch method. This consists in the application of a 1:3 solution of the incriminated arsphenamine to the bare skin of the forearm or upper arm on a patch of gauze approximately one inch square. An impervious covering is

then placed over this moistened gauze which should be at least twice the size of the test patch. At the end of 24 hours the skin beneath the test patch is examined and a positive reaction indicating sensitivity takes the form of marked erythema and vesiculation. A few miliary vesicles scattered on a faint pink background are not necessarily positive. Even though the sensitization reaction be negative, the possibility of a serious grade of arsphenamine sensitivity is not thereby completely eliminated, and it is wiser for the practicing physician to seek advice and use extreme caution in the further management of the case.¹¹⁹

HYPERSENSIBILITY AND IDIOSYCRASY.—There can be no question that there is such a thing as occasional idiosyncrasy and hypersusceptibility to the drugs used in the treatment of syphilis. Such a complication cannot be estimated in per cent, but the observer cannot avoid being impressed with the fact that this category of complications seems abnormally frequent among those whose experience with the treatment of syphilis by modern methods is comparatively small. One is led to suspect, therefore, that inexperienced therapeutic management is at least an important factor in the production of pseudo-idiosyncrasy. The patient who is idiosyncratic to all the drugs used in the treatment of syphilis simultaneously deserves a very full and careful general medical, and at times even a neurologic or neuropsychiatric, examination as well as a dermatological study to determine the underlying factors and the possibility of their elimination. Among the most common causes of pseudo-idiosyncratic reactivity on the part of patients should be mentioned the following:

1. Nervous reactivity produced by fear of the disease, noncomprehension of the instructions for the prevention of reaction, underlying neurosis and hysteria, and psychic and physical trauma and pain inflicted in the course of bungling and sometimes even expert treatment.

2. The cutaneous sensitizing effect of technically incorrect intravenous injection of the arsphenamines which allows part of the first dose of the drug to infiltrate the skin. Sulzberger¹²⁰ has suggested that under no circumstances should the attempt to give the first intravenous injection be stopped by cutaneous leakage. He considers it essential, to protect against future sensitivity, that an intravenous injection of the drug be given immediately, even if assistance for the purpose must be secured.

3. Hyperreactivity simulating idiosyncrasy and sensitivity, but due in reality to technical errors, especially too rapid injection of intravenous medicaments. Great stress should be laid upon the extreme importance, in all forms of treatment for syphilis, of giving intravenous injections slowly. In fact, a needle so small (24 to 26 gauge) that speed is impossible is a legitimate check upon the technic of even the most experienced operator.

Where, in spite of attention to all the details involved in the above items, the patient is still persistently reactive, the practitioner would be well advised to secure expert advice before abandoning treatment or increasing his difficulties by haphazard trials of various possibilities. In connection with the arsphenamines it may be specifically pointed out that a shift from one type of arsphenamine to another, particularly from arsphenamine to neoarsphenamine, or from either "606" or neoarsphenamine to bismuth arsphenamine sulphonate (these representing diminishing grades of reaction-producing qualities), may make possible

the protracted treatment of a patient who at the outset seems very intolerant. Bismuth is a legitimate and, in fact, the best substitute in case of extreme and dangerous reactivity to the arsphenamines; but its relative therapeutic inferiority in early syphilis should not encourage a too ready resort to it in cases of this type. The sensitivity tests as stated, while by no means fully evaluated, give promise of great usefulness in differentiating true from pseudo-idiosyncrasy in the field of the arsenicals.

Local Injuries.—These are largely the result of technical errors and constitute an unhappy commentary upon the totally inadequate teaching of syphilology, not to say of technical therapeutics, in our medical schools, not only of the past but of the present generation. Infiltrated "glass arms," thrombosed veins, sloughs, nodules, abscesses, nerve injuries, not to mention such relative trifles as two or three attempts to enter a vein per injection without the use of a local anesthetic, and the "sieve backs" of patients undergoing lumbar puncture at the hands of inexperienced internes, have a hitherto unsuspected effect upon the popularity of modern treatment for syphilis and the willingness of the patient to undergo the ordeal which it too frequently represents. In a recently reported survey by Pugh,¹²¹ from the writer's clinic at the University of Pennsylvania, on the reasons for the failure of patients to continue treatment until discharged to observation, reactions to treatment stood first among eleven explanations given by patients for their delinquency and lapse. It must be apparent, therefore, that a very large part of the comparative lack of success of this country in controlling the syphilis problem, as contrasted with the more highly organized clinic methods of Europe, is to be laid at the door of inadequate technic. It should follow with equal certainty that all who undertake the treatment of syphilis should acquire as a necessary preliminary an adequate technic of intravenous and intramuscular injection. While it is impossible in a discussion of this length to cover the many details which are essential to accomplishment in this field, the technical high points of both treatment methods are very briefly summarized in the next section on the prevention of complications. It is to some extent possible to improve technic by practice on the manikin and the usability of such a method is being tested in the writer's clinic.¹²²

PREVENTION OF COMPLICATIONS IN TREATMENT FOR SYPHILIS

Preventive measures fall under four heads: first, the taking of a careful history of the effect of the previous treatment each time the patient presents himself for more treatment; second, the examination of the patient periodically for certain evidences of intolerance or difficulty; third, the observance of certain preventive technical detail in the administration of the medicaments; and fourth, the use of general detoxifying measures.

The Question Card.—Prevention of the more serious reactions to treatment is greatly aided by a systematic practice of questioning the patient with regard to his reactions in the interval since his previous visit. So important is each of the questions that should be asked, that the writer finds it a good practice to have them placed on a card bound under a celluloid cover, the card being presented to the patient (if literate) each time, for perusal before the injection is given. It is unwise to allow haste and routine to take the place of deliberation in these

matters, for a very large proportion of serious reactions to arsphenamine particularly can be found on inquiry to have given warning often several weeks in advance of their appearance. The list of questions follows:

QUESTIONS TO BE ANSWERED BEFORE RECEIVING TREATMENT

1. How do you feel?
2. Were you sick at your stomach, or were your bowels loose after the last injection?
3. Any trouble with arm or hip?
4. Is your mouth sore?
5. Any pain down the legs?
6. Did you itch?
7. Did your skin get red or break out?
8. Is it red, itchy or broken out anywhere now?
9. Are you getting up nights to pass water?
10. Is your urine dark or reddish in color?
11. Did you bleed from the gums?
12. Were your bowel movements black?
13. Were your bowel movements white or clay-colored?
14. Were or are there any spots on your skin since last treatment, especially black and blue ones?
15. Are you having a cold? Is it in your head or chest?
16. Is the trouble for which you came in to us getting better or worse, or is there any change?

These questions cover the various possibilities of controllable gastrointestinal reactions from too rapid injection or growing intolerance; errors in intramuscular technic (nerve irritation or injury from incorrectly placed injections); errors in intravenous technic, including venous thrombosis; stomatitis; the prodromes of exfoliative dermatitis and other forms of cutaneous reaction; the early signs of renal irritation; impending jaundice; and hemorrhagic reaction. It is, of course, possible to multiply these questions in determining the character of any symptom that may have developed, but this list covers the most important considerations for general use.

Before treatment is given an inspection of the patient should disclose the following:

1. Condition of the available veins. Palpation is quite as important as inspection, for a thrombosed vein can sometimes be recognized as such only by the way it jumps under the palpating finger and resists compression.
2. Condition of the buttock. Deep induration should be sought for together with any trace of erythema, superficial nodules, tenderness over the sciatic nerve, uncomplicated deep tenderness.
3. Pink stippling or signs of irritability of the skin about the elbow flexures. This will be seen on baring the arm for intravenous injection and may pass unnoticed by the patient.
4. Color of the sclerae. The patient should be viewed in a good light, if possible.
5. Petechiae on the gums, ankles and wrists.
6. Fetid odor of the breath. This suggests bismuth overdosage.

Once in two weeks, at least, the condition of the mucous membranes should be critically inspected, if the patient is on bismuth, for marked

pigmentation is self-revealing and may cause embarrassment even though there may be no stomatitis.

The urine examination has already been described. It should be recalled that polyuria, casts, albumin and blood cells are the order of appearance of abnormal features in the urine of a treated patient. The urine should always have at least a foam test for bile. The value of liver functional tests and tests for the presence of an excess of bile pigment in the blood is still unsettled, but Schamberg and Brown¹²³ have suggested the value of these procedures in anticipating serious grades of hepatic injury. They are, however, too difficult to perform as a routine even in clinics. Blood counts may be indicated for special purposes as in the interpretation of stomatitis and dermatitis. A very marked drop in leukocytes, even though the reaction goes no further, is always of serious prognostic significance and contraindicates further arsphenamine treatment. The hemoglobin should be watched in patients under mercurial therapy and all patients under treatment should be periodically weighed to record the gains in nutritional and general conditions.

Technical Preventive Detail.—INTRAVENOUS INJECTION.—A high degree of proficiency in intravenous technic is obtained only with difficulty and by dint of much practice. An average degree of proficiency may be developed within a comparatively short time by learning a rigorously uniform system of approach consisting of a series of motions which if exactly repeated brings about the desired result in most cases. The essential items in the correct technical approach concern:

1. A satisfactory choice of needles.
2. The position of the arm.
3. A proper application of the tourniquet.
4. The identification and preparation of the vein.
5. A four-point technic of entry.

The Needle.—Due allowance must of course be made for the taste of the individual operator in the selection of needles. In general, however, it may be said that most needles for intravenous work are larger than necessary, have too long bevels which transfix the opposite side of the vein or too rounded points which tear or cut instead of puncturing. Most recently the writer has been using with much satisfaction for syringe work the one-inch hypodermic needle of 24 to 26 gauge, which compels very slow injection and yet is amenable to the four-point maneuver described below. These smaller needles are best used on the more superficial veins, and larger deep ones are better reached by one and one-half inch needles of 22 to 20 gauge. Rustless steel needles are now generally available and are the most satisfactory.

Position of the Arm.—The arm should be extended at right angles to the body with the patient lying down. It should rest on a slightly slanting support at desk level so adjusted that the elbow is really in a state of forced extension. It is wisest to expose the entire arm and neck without constriction. If the patient is allowed to sit, full or over-extension of the arm is none the less imperative.

The Tourniquet.—A broad rubber band, such as an Esmarch bandage, is the most satisfactory tourniquet, though pieces of rubber tubing are frequently employed. They may be held by a hemostat and the hemostat released by the operator or patient, but the band tourniquet

or the pressure cuff of a blood pressure instrument can be controlled by the patient entirely and makes for smoother manipulation. In applying a tourniquet on muscular arms, the compression should not be too great, lest the arterial supply also be partially cut off.

Identification and Preparation of the Vein.—The arm should always be inspected before application of the tourniquet. Palpation may be of more assistance in deciding the vein to use than inspection. Light downward pressure and cross stroking with the ball of the finger will identify even a very white-walled vein. A watch should be kept for previous thrombosis. Poorly developed or difficult veins may be given a satisfactory dilatation by several sharp slaps at the site of injection; by distending the arm vessels by soaking in hot water; and by the systematic daily use of arm gymnastics—all these in addition to the vigorous clenching of the fist after the tourniquet is applied. Much trouble comes from not addressing oneself directly to the vein instead of attempting to operate from the side or at an angle. Thin and flabby-skinned arms, because of imperfect fixation of the skin, may be more difficult than fleshy ones. Scarcely visible veins in the latter type may be much nearer the surface than their appearance and feel suggest. The point for entering a vein should be as near the operator and as far from the heart as possible, so that if a second puncture becomes necessary it may be made above the first to avoid leakage of the injected liquid through the original puncture wound.

The Four-Point Entry.—Whether an unattached needle or a needle attached to a syringe is employed, the four steps for entering a vein are the same.

1. The first step consists in the fixation of the vein with the left hand. This should become absolutely automatic. It is accomplished by drawing downward the skin and tissues of the forearm by the flats of the fingers of the left hand, held palm down. Without this step the vein creeps upward with the needle and a miss is very likely to occur.

2. In the second step the needle, whether guided by the fingers or the syringe, is entered on the flat in the direction of the long axis of the vein. In order to avoid a jerky entry which may traumatize the vein unnecessarily, or pass completely through it, the fourth and fifth fingers of the right hand, holding the needle, should rest firmly upon the forearm of the patient and the movement in introducing the point should be like that of advancing a pen by the use of the fingers instead of the wrist and forearm. If the needle is attached to a syringe, the syringe lies on the palmar surface of the four fingers, clamped to them tightly by the superimposed thumb. The backs of these four fingers are then laid on the forearm and firmly pressed against it. There is sufficient mobility in the patient's skin to allow the syringe and needle to be advanced and retracted by very slight, easily controllable movements without the more awkward and less controlled use of the forearm and wrist. With the bevel of the needle uppermost and with slight downward and forward pressure, the point is pushed through the skin but in the first movement is not permitted to enter the vein. This completes the second step.

3. The third step in the four-point entry consists in the puncture of the upper surface of the vein wall. With the point of the needle just visible as a slight elevation under the skin and with the needle advanced beneath the skin approximately one-half to one centimeter, the butt of

the needle or the syringe is very slightly raised, coincidently with downward pressure of the point upon the roof of the vein. A slight advance of a properly sharpened needle then punctures the vein wall, and the moment this occurs the syringe or needle-butt is again dropped toward the forearm, flattening the needle out along the long axis of the vein, to prevent puncturing the far side of the vessel. The needle is then pushed up the vein for a distance of approximately one centimeter to avoid any possibility of leakage under the bevel and to avoid discharging an irritant too close to the point of trauma.

4. The fourth step is the demonstration of the fact that the needle is completely within the lumen of the vein and entirely free. It consists in releasing the tension on the forearm of the left hand and, while still holding the needle or syringe in position by the right hand resting on the skin, in demonstrating the free flow of blood by pulling backward on the piston of the syringe or witnessing the gush of blood from the hub of the unattached needle, where such is used. The characteristic spurt of the stream of blood across the fluid in the syringe is an absolutely essential concluding test of the correctness of the entry and must always be made before any attempt to inject the syringe contents or other medication. Even with a 26-gauge hypodermic needle it is possible, by pulling backward on the syringe piston, to secure a completely satisfactory return of blood, demonstrating the freedom of the point in the lumen of the vessel.

If, after introduction of the needle, a free flow of blood cannot be obtained, the following procedures may be tried successively to ascertain the difficulty: (1) Depress the needle point without advancing; the bevel may be shut off against the top of the vein. (2) Feel for the needle point with the free hand; if it is still above the vein it can be easily felt. (3) The syringe piston may stick and may be loosened by twisting in the barrel and pulling back. (4) Transfixing of the needle point on the opposite side of the vein, provided the vein has not been punctured, can be remedied by slowly lifting up on the needle point while the needle is withdrawn a short distance; it will come away with a quick snap if it is simply caught in the opposite wall. (5) The needle may then be quickly advanced with the point raised as high as possible, flattening the needle down to the surface of the arm as much as possible. (6) If the above measures fail, the needle may be withdrawn until the point is just short of the skin puncture, and another advance made under guidance of the palpating fingers. If this procedure fails twice, the needle should be withdrawn and retested for patency and the point carefully examined; while this is being done, elevation of the arm with pressure over the vein by a cotton pledget may make it possible to use the same vein again. (7) If leakage of blood into the subcutaneous tissue occurs, begin over at another point; never attempt to inject through a hematoma. (8) Never proceed to inject until certain that the needle is in the vein; to inject a little and ask the patient if it hurts is evidence of lack of skill. (9) One skin puncture may be used for several attempts and every effort should be made to have this one suffice. (10) Cutting down on the vein is absolutely inexcusable in these days, and patients whose veins seem so inaccessible as to suggest the need for such a measure should be sent to an expert. (11) Patients with florid syphilis should always be treated last. (12) The use of the jugular vein, the anterior parietal and other prominent skull veins in heredosyphilitic infants is technically not very

difficult but requires efficient assistance and some experience. The writer has never had occasion to use the superior longitudinal sinus and does not recommend this technic. (13) A few moments spent in adequate survey and preparation may save many minutes, if not hours, of regret. (14) If there has been evident injury to the vein by repeated puncture or by leakage of the drug into the surrounding tissues, cold, or iced, wet applications of salt solution or magnesium sulphate solution may prevent severe reaction and thrombosis.

With reference to the preparation of neoarsphenamine for injection, the most important preventives of complications, it will be recalled, include no shaking; no aeration by squirting of solvent or solution back and forth from syringe to beaker; immediate injection of a freshly dissolved drug; discarding of any drug found the least bit slow in going into solution; and extremely slow intravenous injection of the solution. A rate of one decigram in half a minute is close to the lower margin of safety.

INTRAMUSCULAR TECHNIC.—The technic of intramuscular injection is a matter of considerable moment. Discomfort from this source is one of the principal types of reaction responsible for lapse in treatment. The disposition to blame the drug, precisely as with the arsphenamines, is too often a mistaken one, and the source of the difficulty is rather to be found in the technic of administration. The first essential for a successful intramuscular injection is a satisfactory needle and syringe. The ordinary all-glass 2 cc. Luer syringe is usable for practically all purposes. The needle should be of rustless steel, 2, 2½ or 3 inches in length, depending on the thickness of the fatty panniculus of the buttocks. Twenty-two gauge is satisfactory for most preparations but the heavier ones may require 21 gauge. The thinner preparations require smaller needles, and the smaller the needle the less the likelihood, with any preparation, of leakage along the needle track with the formation of superficial nodules and painful infiltrations. It is absolutely necessary to use the aspiration technic presently described for detecting the presence of the needle point in a vein within the body of the muscle. The needle point should be long-beveled and very sharp, and much discomfort for the patient can be averted by passing the needle on the flat along a piece of sterile absorbent cotton to detect turning of the point, which is indicated by the catching of the cotton fibers as the point passes over them. Needles should be tested from time to time by a forcible bending in order to detect corrosion, weakening and the tendency to break at the junction of hub and shaft. It is because of this tendency to break at this point that needles should never be introduced their full length either into a vein or into solid tissue. They may become lost if the hub breaks from the shaft.

The sterilization of needles and syringes may be accomplished by alcohol, but boiling is preferable.

Injections may be given with the patient standing or lying face down, preferably the latter. Women should remove their corsets, for the snap of a pulled-back girdle, striking the hand, may break a needle. The patient should relax by turning the head away from the operator and "toeing in." Just preceding the moment of making the injection, instruct the patient to take a full breath. This distracts his attention and the entry is usually painless. The practice of making a dagger-like stab seems less preferable than that of resting the side of the hand upon the

skin to steady it, placing the needle point almost in contact with the surface and then, by a quick twist of the wrist, passing the needle through the skin. The remainder of the entry is painless and can be made as a separate movement.

In preparing the injection mass, the directions of the manufacturer should be closely followed. Certain preparations require a warm syringe and all insoluble preparations, unless explicit warning is given, are better for warming in hot water, and absolutely require the most thorough shaking. In bulk preparations, a test of the homogeneity of the suspension can be made by turning the bottle upside down and noting whether any of the precipitate adheres to the junction of bottom and side. Insoluble suspensions should not be allowed to stand in the syringe but should be given immediately.

The buttocks should be used in alternation. An excellent study of the distribution of the injected drug has been made by Shaffer,¹²⁴ who points out that the injection should be deeply intramuscular, that the suspension spreads itself longitudinally along the fascial bundles, that leak-back is prevented by keeping the needle in place for at least a minute following injection, and that the upper outer quadrant is the best site for injection to avoid the risk of injury to the deeper nerves. The writer has always insisted on the inner angle of the upper outer quadrant as the ideal injection point, for it avoids the nerves, avoids trauma from sitting, and the tissues are yet thick enough to escape risk of striking bone.

The site of injection should be vigorously scrubbed with a sponge wet with 90 per cent alcohol, which is entirely satisfactory and preferable to iodine. Preceding the introduction of the needle, precisely as in the case of intravenous injection, the tissues should be fixed and a so-called "valve action" secured by placing the flat of the left hand, palm down, upon the buttock and pressing and pulling downward, in the direction of the heel. When the needle is introduced as above described, the left hand is released and while the right hand holds the syringe still firmly attached to the needle, aspiration is made by pulling on the piston. At least ten seconds of aspiration are desirable and no other method seems quite so effective in disclosing inadvertent entry of a blood vessel. If the slightest trace of discoloration appears in the suspension within the syringe, the needle is withdrawn and a new entry made. At times an operator may enter an unsuspected deep abscess, securing pus or a grumous fluid instead of blood. As soon as the injection is completed the needle is withdrawn, and the left hand quickly pushes upward the stretched panniculus.

An extremely important item following intramuscular injection is adequate massage. This point has been emphasized by Boyd^{124a} and by Colonel Harrison. It is well to massage the site of injection deeply and firmly for at least one minute while the patient still lies on the table, and Colonel Harrison has had very satisfactory results from having the patient massage himself still longer with the use of a species of flat glass pestle, for which the doubled fist is only a fair substitute. Time spent on careful massage materially reduces the incidence of post-injection discomfort. Pain felt down the leg is usually due to encroachment of the injection site or mass upon the sciatic nerve.

A very useful measure for keeping the tissues of the buttock in good condition during a long period of intramuscular injection is the nightly hot *sitz bath*. The patient reads his evening paper sitting in six inches

of very hot water in his bathtub, with his back reclining and his heels on a box or on the faucet handles. Coincident massage or, in the absence of a convenient bathtub, applications of hot wet bath towels are usable but less effective. If a nodule develops, painting with tincture of iodine, if there is no special cutaneous irritability, is sometimes of great service in conjunction with massage. If abscess, which is a very rare complication, develops, it is sterile and a very small opening under local anesthesia will evacuate the contents, which are usually grumous, gelatinous fluid. Occasionally whole batches of a given preparation for intramuscular use will show a greater degree of reactivity than other lots from the same manufacturer. When this occurs it is wisest to communicate with the manufacturing concern and arrange for the return of the product or a more detailed consideration of the difficulty.

TECHNIC OF MERCURIAL INUNCTION.—In spite of its diminishing importance, this time-honored and highly effective method of treatment is summarized here because of its great usefulness in dealing with certain aspects of late syphilis, especially under hospital management or where the patient is remote from a physician. The special advantages of mercury by inunction include its absence of cumulative effect. Two baths and a sweat will, to a large degree, stop the absorption of the drug. Dosage, while not exactly measurable, is none the less effective by a good technic. No method of mercurialization is less injurious to the kidneys in proportion to its effectiveness and none better tolerated by the gastrointestinal tract. Salivation can be controlled by careful mouth prophylaxis and the maintenance of an effective dosage. The disadvantages of the inunction aside from its dirtiness and betrayal of the patient's condition have already been mentioned.

Important technical details in the use of mercurial inunctions include a measured dose dispensed in oiled paper, in capsules or in cocoa butter tablets, of not less than 4 Gm. (60 Gr.) for an adult dose, equivalent to 30 Gr. (2 Gm.) metallic mercury (the official unguentum hydrargyri, which is 50 per cent metallic mercury). The skin should be prepared with soap, water, and alcohol, and carefully dried. Six sites for rubbing may be used each week in rotation, though four will often suffice. Hairy spots should be avoided. The upper and lower flanks, the insides of the thighs, and the back are satisfactory, the last especially, if assistance can be had. Rubbing should be done for 20 minutes by the clock with moderate energy. Too vigorous rubbing may produce irritation. The patient should keep the ointment out of the flexures and in accordance with the old technic should wear the same underwear day and night, taking a hot bath only once a week, at which time he should thoroughly cleanse and powder himself. The rubs are then resumed the following night. A cold shower without soap or rubbing may be taken occasionally in hot weather. Inunctions thus given should be prescribed in courses of 40 to 80. The absorption of mercury by this method is largely through the skin though experimental work shows that the respiratory tract may be an avenue if the drug is left on the skin. Cole¹²⁵ has proposed a so-called clean inunction in which longer rubbing (30 minutes) has been made to take the place of the respiratory absorption of the volatilized excess which may be wiped off as soon as the rubbing is finished instead of collecting on the underwear. The excess is removed from the skin with benzine or gasoline after 30 minutes' inunction. Experimentally, at least, the method gives good results and is much preferable from the

standpoint of the patient's comfort. Calomel by inunction has been tried but seems generally to be conceded unsatisfactory.

GENERAL DETOXIFYING MEASURES.—The first and most important general measure for the prevention of intoxication in treatment for syphilis is that of keeping wide the avenues of elimination. Patients should be encouraged to take **fluids** and to **keep the bowels open** without necessarily purging themselves. Study of the patient's individuality is necessary in this matter and some patients will require almost a routine saline cathartic after treatment, while others must even avoid too much roughage in the diet in order not to keep the bowels overactive or throw them into spasm. The use of castor oil, if there have been less than three bowel movements in the 24 hours succeeding an intravenous injection, is a wise precaution, in part because the drug induces a slight costiveness following the evacuation which prevents a further irritative diarrhea. Other measures have been previously mentioned.

The second step in general detoxification of patients under treatment consists in the use of **routine alkalinization**. Unless there is definite reason to suspect the patient of being hypochlorhydric or achlorhydric, small doses of sodium bicarbonate may be given by mouth from time to time, citrates and fruit juices may be employed and in the event of an impending acute accident, Fisher's solution may be given intravenously. Great care must be taken not to cause infiltration of perivenous tissues with alkaline solutions, for they cause severe sloughs.

The technic of using sodium thiosulphate has already been discussed. The ready prepared solution in ampules is satisfactory, though for a time it was urged that the crystalline salt dissolved in water at the time of injection was preferable. The drug is not particularly satisfactory for administration by mouth, and where rapid effect must be obtained, as in impending arsphenamine dermatitis, mouth administration can be regarded only as an adjunct, and a doubtful one. The continuance of the drug beyond the third or fourth injection and beyond a dosage of 0.5 to 0.75 (Gm. 7.5–11.25 Gr.) must be a matter for individual judgment; but in the majority of cases, as previously stated, the writer has secured what he thought was the maximum effect to be expected from three or four injections on alternate days.

A useful detoxifying measure, presumably an attack upon the possible anaphylactic elements in the action of the arsphenamines, is the so-called **Besredka technic** of dividing the dose of the intravenously administered drug so that nine-tenths of the total quantity is given in a second injection 20 to 40 minutes after the first tenth. The preliminary use of atropine has already been mentioned. These methods can also be used in controlling nitritoid reactions to intramuscularly injected arsphenamines.

Among the more recent methods of detoxification, mention should especially be made of the **intravenous injection of calcium gluconate**, the use of **adrenalin** and **ephedrine**, of **glucose** and of **cesium eosinate**. Calcium, known for its usefulness in heavy metal poisoning, can be employed effectively as the gluconate in 10 per cent aqueous solution, purchasable in ampules for intravenous use. Intramuscular injection is, however, safer. When reaction is anticipated it may be given immediately before the injection, or when it is not, it may be given as soon as reaction is observed. The full dose of 10 cc. is used. The patient should be warned that the sensation of heat and flushing during

the intravenous injection is harmless. The drug can also be used intramuscularly, the entire 10 cc. of a 10 per cent solution being a satisfactory dosage. Adrenalin and ephedrine act particularly upon the vascular manifestations when these are vasomotorial in character. The depressing effect of the arsphenamines, particularly on the suprarenal capsules, can be met in this way, and this probably establishes a part of the rationale of the treatment. The use of adrenalin has already been mentioned, but ephedrine was studied by Stokes and McIntyre,¹²⁰ who found that it was most effective in preventing postarsphenamine nausea (23 out of 32 cases), and that its general effectiveness in dealing with headache, vertigo, nausea, urticaria, pruritus, and repeated nitritoid crises was approximately 60 per cent. The dose is 50 mg. in capsules twice or three times a day for one or two days preceding or partly including the day of the injection. The disagreeable inclination to cough and choke, probably an abortive form of nitritoid reaction in certain patients, is very well controlled by the previous administration of 50 mg. of ephedrine by mouth on the morning of the treatment day.

Glucose solution can be used as the menstruum for the preparation of neoarsphenamine for intravenous injection, but the recent work of Craven on the failure of carbohydrate to protect the liver may make this inadvisable. Its use in the treatment of early exfoliative dermatitis has already been mentioned (10 to 20 cc. of a 50 per cent solution). Oliver and his coworkers have recommended a gelatine solution for buffer in arsphenamine administration, but nothing practical seems to have developed thus far from the suggestion.

One of the most useful ways of dealing with a tendency to reaction from a given drug is to change to one of the alternates of the same type but of slightly different chemical composition. This method is often quite successful with the arsphenamines, the order of diminishing toxicity being: sulpharsphenamine, arsphenamine, neoarsphenamine, bismuth arsphenamine sulphonate. This statement, however, does not apply to the hemorrhagic accidents or true exfoliative dermatitis which cannot be avoided in this way. The suggestions with reference to bismuth salts have already been made. In the case of double compounds, such as bismuth arsphenamine sulphonate, it is necessary to determine by patch test which ingredient is responsible for the apparent sensitivity, for Schoch¹²⁷ has described reactivity to the arsphenamine radical in bismuth arsphenamine sulphonate and O'Leary¹²⁸ has reported dermatitis following the use of bismuth.

CERTAIN COLLATERAL CONSIDERATIONS IN TREATMENT

This subject as ordinarily treated would include especially the effect of treatment upon the infectiousness of the disease, the transmission of the disease in marriage and to children, the personal hygiene of the syphilitic patient, focal and intercurrent infections, the mental state of the syphilitic patient, syphilis and intercurrent disease, the therapeutic test, the determination of cure, and the general effect of treatment on the status of the patient. It is here only possible to deal with these considerations in summary and brief fashion. The control of infectiousness is dealt with in the section on the treatment of early syphilis, and the transmission of syphilis in marriage and to the child is discussed in the section on prenatal syphilis.

The Decision When to Treat and When Not to Treat.—The influence of age, time and status factors in the management of a syphilitic infection has been touched upon, but a little added emphasis is needed in consideration of the critical decisions connected with patients who have long-standing infections which have or have not been treated in the past. To reduce the matter as far as possible to rules of thumb, the following principles are offered:

1. Infectiousness or potential infectiousness is invariably ground for vigorous treatment, including the use of an arsphenamine under proper precautions. This makes the problem confronting the physician who deals with early syphilis a comparatively simple one. He must treat at least to noninfectiousness if not to cure.

2. The majority of patients should be treated well beyond the disappearance of all active symptoms and signs of the disease if it can be done without demonstrable ill effects. This includes not alone the disappearance of visible lesions, but complete serologic negativity on blood and spinal fluid.

3. A careful distinction should be drawn between scars and evidences of active progress. One should not attempt to treat tabes until the knee jerks are recovered or aortic regurgitation until the murmur disappears.

4. The influence of age and time factors in the latent case is discussed under Risks vs. Benefits.

5. In the case of a patient with a definite, satisfactory history of syphilitic infection, but with desultory or apparently inadequate treatment resulting in symptomatic and serologic negativity, it seems on the whole wisest not to run the risk of arousing the process by further treatment provided absolutely no sign of activity can be discovered on the most painstaking examination. Protracted if not life-long observation is usually, but not invariably, the wiser course. If the history and previous evidence of the disease are thoroughly convincing, if the patient is young and the lapse of time necessary for active cardiovascular lesions to develop has not yet passed, it may in occasional cases be advisable to treat even the serologically and symptomatically negative patient "for life insurance." In the case of a woman with a clear-cut history and previous inadequate treatment, the possibility of a lighting up of the infection during pregnancy must be considered, and treatment during this period on empirical grounds for the protection of the child has very strong support.

6. Two years of complete symptomatic and serologic negativity following the cessation of treatment of a reasonable degree of intensity justifies, in the main, the placing of the patient on yearly observation. Again the disease duration and the patient's age are factors of much importance.

7. There are, of course, positive, contra-indications to treatment. A patient with a probable malignancy which is practically certain to cause his death before the syphilitic infection can overtake him should be treated only with a view to increasing his general symptomatic well-being. Active pulmonary tuberculosis in general takes precedence over syphilis in treatment unless the activity of the syphilis directly endangers the patient's contacts. On the other hand, judicious treatment with the arsphenamines, especially after fever has subsided under rest, may greatly benefit the patient with coincident pulmonary and other forms of tuberculosis through nonspecific as well as specific effect.

Syphilitic infection appearing in the course of other constitutional conditions—such as pernicious anemia, diabetes, exophthalmic goitre, etc.—may have to be treated within the limits of tolerance imposed by the general condition. Goiter may reduce tolerance of arsphenamine and interdict iodides. On the other hand, there could be nothing more inexcusable than to forget the complicating syphilis, as too often occurs, or to regard it as a triviality merely because for the moment it is overshadowed by another and more acute medical or surgical condition. Cases of this type constitute the medical scandals of syphilologie practice and are all too numerous. To see a case of epithelioma of the lip in which the Wassermann reaction is positive, operatively cured, only to develop an enormous aneurysm ten years later because his syphilis, although recognized at operation, was regarded as inactive or a matter of small moment, is to witness the overshadowing of syphilis by surgery. To see the crises of *tabes dorsalis* appear a decade after the recognition and ignoring of a syphilis as a complication of exophthalmic goiter, is to witness the complete defeat of preventive medicine with respect to syphilis.

Personal Hygiene of the Syphilitic Patient.—The syphilitic patient receives most of his impressions on the matter of personal hygiene from what should be the content of his first interview with his physician. After outlining the situation with reference to infectiousness, he should be advised not to kiss; to sleep alone; to trust the marital partner with the facts; to have his own towels and dishes at home and when away to eat where the dishes are likely to be scalded; and never to use another person's shaving tools, cup, dipper, spoon or eating utensils, pipe or cigarette holder or any other toilet article. Every open sore should be considered infectious until the physician is consulted; and the patient should be instructed to watch for "patches," cold sores, chancres, pimples, chafes, and "piles." Sexual intercourse should be only as permitted by the physician, in accordance with the principles previously discussed, and those concerned with the treatment of the patient to non-infectiousness. It is advisable for the patient not to smoke, but the injunction is usually disregarded. The correction of worry and mental strain, loss of sleep, overwork, undernutrition, and insistence on a reasonable standard of exercise and similar details contributing to good hygiene under any circumstances are appropriate to the management of syphilis. Certain items deserve additional consideration.

Trauma and Overstrain.—Resistance to syphilis is a rather unaccountable affair; and one meets patients in whom one finds every excuse for the most severe complications, yet none the less they have escaped unscathed. On the other hand, splendid specimens of physical and mental integrity are too often hurried over the road to paresis. Trauma is particularly important in bone lesions, in the development of the trophic joints of *tabes*, and in the onset of clinical symptoms in an otherwise latent paresis (head trauma especially). Every tabetic should be warned against the danger of developing Charcot joint following a sprained ankle, wrenched knee, and so forth. The influence of intercurrent and focal infections is, in general, deleterious. Accordingly, it is advisable for syphilitic patients in the later years of the disease to keep away from cold and wet, and to seek mild and sunny climates whenever circumstances permit. The tendency to nonresolution with gummatous pneumonitis as the sequel of pneumonia is probably evi-

dence of an attack by syphilis upon a *locus minoris resistentiae*. Nervous overstrain seems at times to predispose to the unfavorable progress of a neurosyphilis, but it should be recalled in this connection that unwelcome rest with enforced introspection and worry is sometimes more unfavorable in its effects than a reasonable degree of happy and pre-occupying activity. Rest has a general nonspecific value in the management of syphilis, notably in cardiovascular disease, though here the effect is rather upon the heart than upon the syphilis. Rest in bed is otherwise rarely required in the control of the disease. On the other hand, ability to relax, if it can be accompanied by the ability to forget or by a restoration of hope and confidence, is a very important therapeutic aid.

Focal and Intercurrent Infections.—Intercurrent infections occasionally may have paradoxical beneficial effects as in pyelitis accompanied by high temperature, which I have known to affect in a strikingly favorable way the course of a case of general paresis. The influence of focal infections is almost invariably unfavorable. The lightning pains of the tabetic, an irritable kidney, intolerant of even mild treatment, a tendency to develop arthralgias and arthritis on the exhibition of mercury, and a general asthenia with very little tonic effect from even the more stimulative forms of treatment, are common complications of chronic focal infections. At times it is necessary to pursue these systematically through the gamut of tonsils, teeth, prostate, gallbladder, and colon until the weak spot is found and repaired or done away with. Particularly with reference to dental focal infections, it is better to be a little too radical than ultraconservative. The writer has known teeth which, though they passed competent dental examination and x-ray, proved on removal to have been the focal infectious basis of persistent and exasperating symptoms, particularly in tabes. Weight is a very useful index of progress and a gain is to be desired in practically all cases except older patients with a risk of cardiovascular insufficiency. The best gains under the older methods of treatment were made during rest intervals and constituted a strong argument in favor of intermittent treatment. With the tonic action of the arsphenamines, and particularly bismuth arsphenamine sulphonate, the gain is often transferred to the course of treatment itself. A mere gain of weight in cardiovascular or hepatic syphilis may mean accumulated fluid as an unfavorable complication rather than a bona fide gain in well-being.

Dietary Management.—In spite of the claim which the writer once encountered and which has since been echoed through cultist sources, a milk diet is not the ideal means of reversing a positive blood Wassermann reaction. Nourishing food, with proper attention to the bowels particularly, is all that hygiene requires. In the obstinate intestinal atony of tabetics, in addition to diet, a medicine ball or an eight to twelve pound shot rolled over the abdomen, and rectal injections of two to three ounces of olive oil every evening, to be retained, are at times of material assistance when not contraindicated by definite gastro-intestinal or abdominal pathology. For renal irritation or insufficiency, the low-protein salt-free diet is at times serviceable though less so than one would expect.

Alcohol and Other Stimulants.—In general alcohol is of no advantage to the syphilitic patient except at times in the form of a light wine for carminative purposes. The use of the stronger drinks is to be depre-

ated as distinctly injurious and as placing an unnecessary load on the heart, kidneys, liver and nervous system. The dipsomaniacal syphilitic with his periodic bursts of besotted intoxication is the most inveterate relapser that the writer knows in syphilologic practice. The general principles applying to the use of other drugs and stimulants are those of medical common sense.

Mental State of the Syphilitic Patient.—Depressions, anxieties, phobias, and morbid terrors which beset the patient who knows that he has syphilis are too frequently dismissed by physicians as merely syphilophobic or hypochondriacal. The sense of stigma is particularly vexatious and difficult to deal with but can usually be lightened or entirely done away with by a sympathetic talk. The striking beneficial effect of such treatment is frequently apparent and some patients fail to make any real general gains in well-being under therapy until it is applied. True anxiety neuroses with syphilis as a background must be painstakingly unraveled and set right.

One of the worst sources of trouble is the tradition of secrecy which leads physician and patient to collaborate in concealing the presence of the disease from the marital partner. It is conceded that there are circumstances in which it is unnecessary for the partner to know the facts, inasmuch as they do not involve the issue of the transmission of the disease or the economic status of the individual concerned. On the other hand, in the majority of cases complications are almost certain to ensue on an attempt to combine intensive modern treatment with an artificial secrecy. In the large majority of these cases the tactful preliminary management of the physician can bring about an understanding between husband and wife in which the facts are kept in the background so far as the origin of the infection is concerned, and the patient given the benefit of the doubt. The rejuvenating effect of such a resort to honesty in many situations is almost the equal of the arsphenamine miracle itself. It should be borne in mind, however, that before any attempt is made to communicate facts to other persons than the patient, the diagnosis must be absolutely substantiated.

Local Treatment of Syphilitic Lesions.—It has been said already and should be reiterated that the first principle applying to the first lesion of syphilis is **no local treatment**. In other aspects of the disease the response of surface lesions to the arsphenamines is so rapid and, even under bismuth, is so satisfactory that there is no occasion for the use of any elaborate local measures. Several days of **wet dressings** with potassium permanganate solution (1:4000) or with boric acid solution usually result in a prompt granulating of denuded surfaces followed by a rapid growth of epithelium. The noncontractile character of the syphilitic scar makes the deformity usually less than is expected. Osseous syphilis may require the removal of sequestra before healing will take place, and in the case of osteitis of the skull, special surgical technic may be called for. Operations on bone, however, should not be performed until after treatment control is thoroughly established lest they extend the lesion.

Operations on gumma, whether recognized or unrecognized, belong to the past and are practically inexcusable at the present time. In the majority of cases the incision of a gummatous infiltration results in rapid extension. A possible exception to the rule just given is the neces-

sity for the removal of fibrous gummas of the meninges or brain which act as tumors.

Principles Underlying the Therapeutic Test.—1. A therapeutic test for syphilis should not be performed for a vague and indefinite group of symptoms such as loss of weight, malaise, headache, and the like. The results, owing to nonspecific action, are not trustworthy.

2. No therapeutic test should be performed on genital lesions. The existence of syphilis should be proved or disproved as described in a subsequent section, by the dark field, Wassermann follow-up, complete examination, and observation; or the patient treated as having a diagnosed syphilis.

3. Tuberculosis responds nonspecifically to the arsphenamine treatment for syphilis, and iodides are noted for their nonspecific effects on granulomatous processes in general. Accordingly, neither drug should be used in an exacting therapeutic test for syphilis, especially where the differentiation of tuberculosis and other granulomas is involved.

4. Therapeutic tests to differentiate tuberculosis from syphilitic processes should be made with mercury or bismuth.

5. The therapeutic test implies observation during the test. It is at its best on visible lesions and its value is proportional to the definiteness and measurability of the symptoms and of the improvement which takes place in them.

6. In late visceral syphilis, and especially in cardiovascular lesions, symptomatic improvement may establish the diagnosis in spite of the fact that no change may occur in the structural signs, but such observations must be carefully distinguished from nonspecificity.

7. Spontaneous improvement in some conditions may produce the mistaken impression of a positive therapeutic test as, for example, in multiple sclerosis and some heart conditions.

8. Therapeutic tests for syphilis may be obscured and rendered uninterpretable by the simultaneous use of other forms of treatment, such as the x-ray to a mass of glands or other lesions, the removal of focal infections, local applications and rest, salicylates in joint involvements, and so forth.

9. Not less than four arsphenamine injections are necessary to a therapeutic test which is to depend on symptomatic improvement for a positive decision. An exception is gastric syphilis, in which the symptomatic response is usually immediate.

10. A therapeutic test offers the opportunity for a provocative procedure or a Wassermann series. The test may be taken daily for the first week, or weekly for the first four weeks.

11. Due regard must be had for risk of therapeutic shock and paradox, and for contra-indications to certain drugs in selecting therapeutic test methods.

12. If the question of operable malignancy versus syphilis is raised, surgery has the right of way (except for a single sterilizing dose of arsphenamine), and the patient should be explored before a therapeutic test is considered. This is also true in an undoubted syphilitic patient if the question is raised as to whether a visceral picture is due to operable malignancy or to syphilis. If the condition is inoperable, treatment for syphilis takes first place.

13. In a cutaneous nonulcerative lesion with a negative blood Wassermann reaction, two arsphenamine injections at the most should pro-

duce practically complete involution in 10 to 14 days. If more injections are needed, the test may be indeterminate because of arsenical nonspecific effect. Extensive ulcerative lesions may require special judgment.

14. Therapeutic flare-ups (Herxheimer) should be watched for as evidence of syphilis if not contraindicated on special grounds. Insist on daily observation the first week.

15. A symptomatic constitutional flare-up may also occur. Both may be delayed in bone and neurosyphilitic cases.

16. As examination for evidence of syphilis becomes more complete and critical, there is less and less need for uncontrolled therapeutic tests.

17. A positive therapeutic test is part of a complete course of treatment. It should not be dropped when the positive diagnosis is made.

18. An indeterminate therapeutic test should not be terminated with arsphenamine, for the immunity which has kept the disease concealed may be broken by the inadequate treatment. At least a course of 10 or 12 injections of bismuth or 40 inunctions of mercury should be given.

Medical Prophylaxis of Syphilis.—Prophylactic treatment may be local or systemic. Local prophylaxis for syphilis is now universally combined with prophylactic treatment for gonorrhea. Two types are in existence. The one for personal use is known as **packet prophylaxis** and the organizational type in use in the armies and navies of the world is known as **station prophylaxis**. Extended experience has shown that a 33 per cent calomel ointment in a base of benzoinated lard and lanolin is the most satisfactory preparation for the prevention of infection by local treatment. Two per cent protargol or 10 per cent argyrol solution is employed in station prophylaxis, while phenol, camphor, trichresol and thymol are used in packet prophylaxis as gonococicides in conjunction with the calomel ointment. It has been repeatedly demonstrated that the success of any prophylactic technic is dependent on the promptness of application following exposure. The effectiveness and importance of station prophylaxis in military bodies is no longer open to question and has been fully established by the experience of the late war. Colonel Ashburn¹²⁹ has estimated that 1 man in 30 who did not take prophylaxis developed venereal disease, while only 1 man in 90 who took prophylaxis became infected. It is important, however, to emphasize the great superiority of station prophylaxis as compared with the ordinarily applied packet prophylaxis. The standard army directions for station prophylaxis are as follows:

DIRECTIONS FOR GIVING PROPHYLAXIS

1. The patient will urinate and proceed as follows:
2. Wash hands thoroughly in warm water and soap and afterward rinse them in plain water.
3. Roll up shirt and drop trousers and drawers to the knees.
4. Pull back foreskin and wash head of penis very thoroughly with warm water and liquid soap, great care being taken to cleanse the under-surface around "G string" and just back of head in the furrow. After this, wash the body of the penis, and adjacent parts of the body. A clean basin with warm water, liquid soap, and a piece of gauze for scrubbing will be used. The basin after use will be washed with water and then filled with bichloride solution 1:1000 and allowed to stand for at least 30 minutes before being used again.

5. While the foreskin is drawn back, wash the penis, particularly the head, with warm bichloride solution 1:1000. This may be done by having the solution poured over slowly, or by washing in a clean basin half full of the solution. This process should require about three minutes.

6. The attendant, without touching the penis, will inject slowly about one teaspoonful of a 2 per cent solution of protargol or of a 10 per cent solution of argyrol into the penis and, as the syringe is withdrawn, he will direct the patient to close the opening to the penis with the thumb and forefinger, and retain the solution for five minutes.

7. Pull back the foreskin and rub one teaspoonful of calomel ointment all over the head of the penis and the inner surface of the retracted foreskin, being careful to rub it in thoroughly on the under-surface around the "G string" and in the furrow behind the head. The rubbing in of this ointment should continue for three minutes. After this the surplus ointment will be rubbed well over the shaft of the penis.

8. The foreskin will be drawn forward and the penis wrapped in a piece of toilet paper and the patient directed not to urinate for at least four hours.

9. If more than three hours have elapsed since exposure, the patient, after having the regular prophylaxis, will be directed to report twice a day for two days for injection of 1 per cent solution of protargol. This will be held in for ten minutes.

Systemic Prophylaxis with Arsphenamine.—The value of systemic prophylaxis through the utilization of the spirillicidal activity of arsphenamine is as yet undecided. Observers of undoubted competence feel that the method offers more dangers than advantages and that its users are left in a state of uncertainty with reference to their possible infection, which is more serious than waiting for the outcome of the exposure. Moore has contended¹³⁰ that even though arsphenamine prophylaxis be applied, it is desirable for the patient to approximate the routine of early treatment for syphilis and at least to have serologic and spinal fluid controls similar to those for a known infection. Recent experimental studies discussed in the earlier part of this presentation seem to bear out the possibility that prophylaxis may appear to be effective without actually being so, and that a person may become an unwitting carrier of syphilis even though he believes himself to be fully protected. Physicians who themselves require, or desire to use, this method of protection should recognize the importance of time as a fundamental principle and make no attempt to utilize arsphenamine prophylaxis after 24 hours. Three successive injections of neoarsphenamine of 0.45 to 0.6 Gm. each, given on three successive days, are probably the optimum requirement. A preliminary blood Wassermann reaction should be taken and the blood Wassermann reaction should be repeated monthly for at least a year together with observation for the development of any symptoms. It is a serious mistake to take prophylaxis later than 24 hours after exposure to the risk of infection, for failures under these conditions have been reported.¹³¹

THE PROBLEM OF "CURE"

In defining syphilis and in discussing the immunologic background of the disease, the writer has tried to make it clear that the use of the term "cure" in connection with syphilis at the present day, despite the

enormous advances in treatment control, is still an expression of faith rather than a statement of fact. Practically all the observed phenomena of the disease throughout the lifetimes of patients thus far studied could be satisfactorily explained, including the fact of a lifelong latency, by the discovery of a granular or ultramicroscopic stage in the life cycle of the *Spirochaeta pallida* and the induction, by treatment, of a prolonged latency as posited by Warthin. It is proper to state, then, that there is today, so far as man is concerned, no proof of cure except observation. A lifetime free from complications of the disease, and nontransmission to others, is the utmost which the clear-sighted syphilologist can offer his patients. It is possible to say that the reexamination of treated patients thus far undertaken by the principal clinics of the world has indicated a presumption of complete arrest in early cases ranging from 65 per cent to 100 per cent, depending upon the rigidity of the reexamination criteria and the stage of the disease at which treatment is begun. In the fully established infection which has reached the stage of serologically positive latency, and in all subsequent phases of the disease, including every clinically detectable structural complication, it is disingenuous and unwise to use the term "cure." The patient constantly presses for a definitive statement on this matter. The only way to meet his demands is by an absolute frankness which acknowledges the nondeterminability of cure, the probability that asymptomatic latency is all that can be expected, and the certainty that observational control should extend throughout life. The large majority of patients, excepting perhaps that small group whose sense of stigma demands the "purification" of their blood, are well content to accept the assurance that, with coöperation on the part of themselves and intelligence on the part of the physician, lifelong freedom from symptoms and assurance of noninfectiousness can be extended to at least 90 per cent of patients who have acquired the disease. In order to analyze certain of the elements entering into the observational control of a syphilitic infection, the following items are specifically discussed: (1) serologic control through blood serologic tests and spinal fluid examination; (2) the worth of the provocative procedure; (3) the fixed positive blood Wassermann reaction; (4) symptomatic progress with negative serologic tests; (5) intuition and the biology of the disease; and finally, (6) a suggested scheme for observational control.

Serologic Control.—The weakening or diminution in intensity of serologic reactions by both the Wassermann and precipitation procedures under the influence of treatment is, of course, too well known to require discussion. Certain misconceptions, however, require correction. The precise meaning of a positive or a negative blood Wassermann reaction is as yet far from understood so far as its value as an index of activity of the disease is concerned. With the increasing acuteness and sensitivity of serologic tests, many patients who by the older procedures were regarded as serologically cured are turning out to be merely examples of a reduced intensity or weaker degree of positiveness in their serologic tests. Wile and Hasley⁵⁶ pointed out, even before some of the newer methods were developed, that it is easily possible to raise the sensitivity of serologic tests to the point where few, if any, patients who have once had a syphilitic infection can ever be indisputably and continuously negative. Accordingly, the meaning attached to a series of negative serologic results in any given case is dependent to no small

extent upon the method of testing employed. The Kolmer and Kahn tests meet all practical requirements in this regard and patients who are continuously negative over a long period of time by these two procedures may be accepted as "serologically inactive." They are not, however, by this fact, to be described as cured.

The first bar to the use of a continuous series of negatives on the blood as evidence of cure lies in the indisputable possibility of symptomatic progress in spite of serologic negativity. Some of the most disconcerting examples of this state of affairs have been recognized in recent years in the form of gradual development of signs of cardiovascular syphilis in patients who have been for long periods serologically negative. The serologic negativity of such cases is, to be sure, not quite so perfect as that of the ostensibly cured case, and one is able, by frequent repetition, to "pick up" occasionally partial or even strong positives which indicate that the threshold has been simply raised rather than abolished. Neurosyphilis likewise affords a number of excellent examples of symptomatic progress due to isolated lesions which leave no indication in serologic positivity, either in the blood or the spinal fluid. Accordingly, it is impossible for any series of negative tests by any procedure to be accepted at the present day as final and conclusive evidence that the disease has been completely abolished in a given individual.

Emphasis should likewise be laid upon the fact that a provocative procedure may fail entirely to bring to light a positive serologic test on the blood in spite of the fact that the disease is still progressive. It has even been possible to find examples in the writer's own experience of active infectious lesions following a negative provocative procedure. Accordingly, while the provocative test, performed either as the once-a-week series for the first four or five treatments of the new course or as the once-a-day procedure for one week following the first arsphenamine injection, may fail to reveal the presence of the disease, the provocative procedure still has a certain amount of value in detecting a revival of serologic activity.

The relative worth of the Kolmer or Kahn test as an index of serologic response, particularly in early syphilis, was studied on the writer's service by Gilman and McIntyre,¹² who reached the conclusion that either procedure is a satisfactory means of measuring treatment progress serologically, but that both procedures are more wisely used to cover each other's possible discrepancies.

The spinal fluid examination is, as has already been explained, a necessary part of the serologic control of every patient under treatment. The question of chief concern is that of the frequency of repetition of a spinal test in a patient under observation. The writer believes in general that the negative spinal fluid examination at the close of a properly conducted course of treatment has considerable value as an assurance that the nervous system either is not involved or has responded satisfactorily. None the less, it must be pointed out that this is not invariably the case. For example, the case has been cited from the writer's own files in which a negative spinal fluid examination was followed by a hemiplegic recurrence and a subsequent "red flag" picture in the spinal fluid. Alleged reinfections or superinfections, to be discussed later, may also be accompanied by involvement of the nervous system which may be misinterpreted as neurorelapse; and relapse itself.

involving the mucous membranes and skin or taking the form of recurrent secondaries, may be accompanied by involvement of the nervous system even though this group of structures may have escaped the first or original distribution of spirochetes at the onset of the infection. It must be recalled, too, that the *Spirochaeta pallida* has been found repeatedly in the negative spinal fluid, so that no generalization in regard to the significance of negative spinal fluid tests can safely be made absolute. Perhaps a fair compromise with the practical necessities of the situation can be found in the principle of repeating a spinal fluid examination of which the initial findings were negative, once, in the absence of symptoms—a year after the first examination and after all treatment has been stopped.

The question is very properly raised as to the extent to which a positive blood serologic test can be accepted in lieu of a spinal fluid examination. Negative blood serologic tests do not prove the freedom of the central nervous system from involvement. Positive tests, however, appear in the large majority of patients who have neurosyphilitic involvement in the earlier months of the disease. The appearance of a positive test, therefore, after a series of negatives may, among other things, indicate impending or actual involvement of the nervous system or neurorelapse. On the other hand, it is impossible to determine whether the reappearance of the positive indicates an involvement of the nervous system without a spinal fluid examination. The reappearance of a positive in a series of negatives is therefore only a "suspicion-arouser" and not an evidence of recurrent neurosyphilis. On the other hand, as will be reëmphasized in the next paragraph, the persistence of a positive blood serologic test in spite of treatment raises a strong clinical presumption that the nervous system is involved, at least in the earlier months of the disease. A spinal fluid examination should therefore be invariably carried through in all patients whose blood Wassermann proves irreversible under a reasonable amount of treatment. It is essential to stress again the fact that a Wassermann or precipitation test alone on the spinal fluid is not sufficient for the determination of presumptive neurosyphilitic involvement. In a patient who has syphilis, let it be reiterated, even a slight rise in cell count above normal is best regarded as significant even though the spinal fluid Wassermann is negative.

The Fixed Positive Blood Wassermann Reaction.—The point on the scale of treatment at which a blood serologic test can be regarded as having given evidence of fixity or irreversibility cannot, of course, be specified. Busman and the writer in studying a series of these cases¹³³ adopted a minimum of 12 injections of "606" and 90 mercurial inunctions as a sign of Wassermann-fastness. Accepting the "noninfectiousness basis" disclosed by the coöperative clinic investigations of the American League of Nations group,¹³⁴ 20 injections of an arsphenamine and 20 injections of a heavy metal might conceivably be accepted as the starting point for interpreting Wassermann fastness. So large does the positive Wassermann loom, however, in the minds of the majority of practicing physicians that patients are usually not regarded as having irreversible serologic tests until they have had much more than this minimum standard of treatment. The following points must emphatically be borne in mind with reference to the so-called fixed positive type of case. The resistance offered by the serologic tests should not be al-

lowed to stand alone as an indication for the continuance of treatment. It may be expected that the most "fixed" Wassermann or precipitation test will waver somewhat in a series of performances and that many patients will show resistance rather than absolute fixity. Serologic tests should in no case be considered alone as evidence of the need for treatment. To treat a positive Wassermann as such without further study is the height of amateurishness in syphilologic practice. Before deciding that a positive serologic test is monosymptomatic, fixed and irreversible, it is absolutely necessary to interpret the patient clinically by the most painstaking and complete physical examination, and to examine his spinal fluid. Cardiovascular syphilis and neurosyphilis in particular most often lie in ambush behind the screen of a seeming latency with a positive blood Wassermann or precipitation. It is, therefore, an evidence of inexperience with the disease to ask what therapeutic procedure should next be adopted in a supposedly Wassermann-fast case, until the cardiovascular mechanism has been carefully studied and a complete examination of the spinal fluid has been made. Until cardiovascular and neurosyphilis have been painstakingly eliminated, it is impossible intelligently to discuss the treatment of a given case of supposed serologic "fastness."

Granted that clinical evidence of the disease is limited to blood serologic tests that will not reverse under the amounts of treatment above described, the following principles become applicable:

1. The serologically fast case should be observed at intervals throughout life.

2. The treatment of such a case should be directed less toward overcoming the resistance offered by the serologic findings and more toward watching the tolerance of the patient and envisaging the aims appropriate to his age, the duration of his infection and his general welfare. Treatment for "life insurance" is the appropriate type of procedure for such a case. If tolerance permits, in view of our ignorance of possible complications, a year or 18 months of reasonably thorough treatment followed by observation should meet the indications. Even with this proviso, there is no question that the majority of these monosymptomatic fixed positive Wassermann cases will be overtreated.

3. Successful reversal of a fixed positive serologic test depends first of all upon treatment regularity. Sporadic efforts, lapse, and nonoperation almost invariably prevent a satisfactory outcome.

4. Reversal of a resistant group of blood serologic tests is dependent apparently more on variety of therapeutic attack than on the overintense use of a single method. Accordingly, the patient who has what seems to be a fixed and monosymptomatic positive Wassermann or precipitation test should have his treatment methods varied to include at least two or more forms of the arsphenamines together with mercury, bismuth, and iodide in such combinations as his tolerance permits. The value of using two or more synergistic methods simultaneously, such as an arsphenamine, bismuth and iodide, or an arsphenamine, a soluble mercurial salt and intravenous iodide, also deserves consideration. It is a question whether fever therapy should be used merely for the purpose of reversing a resistant Wassermann test in an otherwise asymptomatic subject. The writer's own experience with nonspecific methods of this sort has hardly been encouraging, for the tendency to relapse after a sufficiently long period of observation seems very marked. It is more

often the change of method than the antisyphilitic value of a particular drug that seems to be responsible for the ultimate reversal of so-called fixed positive cases. In general a proportion of reversal ranging from 25 per cent to 50 per cent is the best that can be expected by any of the present day procedures.

Symptomatic Progress with Negative Serologic Tests, and in Spite of Treatment.—It must never be forgotten that the very best and most energetic treatment as well as the worst and most unsystematic, may be a failure in an unpredictable proportion of patients who have syphilis. Cardiovascular disease probably furnishes the best examples of this slow progression of the degenerative process in spite of a persistently negative blood and reasonably energetic treatment, as already stated. The writer has now had under observation for periods as long as 12 and 14 years patients who have never since the early stages of their disease or the earlier months of its recognition had positive serologic tests. He has seen certain of these patients slowly progress to serious grades of cardiovascular, visceral, and neurosyphilitic damage in spite of treatment and beneath an unruffled serologic surface. For example, a patient seen in his primary stage in 1917 has in the intervening 13 years developed both syphilis of the liver and syphilis of the aorta without having on a single occasion developed a positive serologic test at the hands of a variety of laboratories and individual consultants. Another case, first seen with an active neurosyphilis, has in 14 years of observation developed symptomatic tabes even during the progress of his treatment and has subsequently, in a rest interval of several years, developed an isolated lesion of the optic nerve. Throughout this entire period of observation since the first several months, the patient has been serologically negative. On the other hand, as a contrast, the writer has had under observation for an almost equal length of time a patient with a strongly positive blood Wassermann reaction and a stationary aneurysm who literally owes her life and present good health to the exercise of a conservative moderation in her treatment. This type of "I-had-a-case" evidence cannot, of course, be made a substitute for statistical evaluation of the presumptions in the matter; but it does, none the less, emphasize the fact that, particularly in the later stages of the disease, each patient is a law unto himself and that observation at reasonably frequent intervals takes overwhelming precedence over merely serologic data.

Intuition and the Biology of the Disease.—There enters into the appraisal of every patient with respect to the question of activity versus arrest an indefinable element of intuition. This intuition is acquired through long experience with the biology of the disease and is often the basis of accurate prognostication and correct judgment as to the needs of the particular case. The consultant learns slowly and in a half-conscious way what to expect of the disease in subjects of varying habitus and under varying conditions. This slowly accumulated intuitive evidence or appraisal of the individual case is, of course, one of the strongest reasons for urging the patient to remain under one consistent direction throughout the entire course of his infection and his life. When, as in some decisions, a broad, as distinguished from an individual or personal, knowledge of the biology of the disease is required, a consultation center and a syphilologist must be sought.

The difficulties that beset the majority of physicians in the effort to maintain observational control of the syphilitic patient are to some extent

inseparable from the nature of the disease. Absence of symptoms and a series of previous negative blood tests appeal to the patient as the poorest possible reasons for keeping in touch with his physician. Too often the patient, weary of his physician's reiteration and retreating, inclined to seek change or what he considers better and more disinterested advice, or taking the matter into his own hands by seeking Wassermann tests from laboratories and other agencies which will perform them without medical control, gets absolutely out of hand by the end of his second or third year. This tendency, recognized the world over, is the best argument for supplying the individual patient with a record book or statement of his findings and treatment which may be shown to any medical adviser to whom he may present himself. Whether or not the physician first responsible for a given patient with syphilis believes that he can keep him under prolonged control or not, it is essential for him to do the following things:

1. Make a thorough base-line physical examination with particular attention to the cardiovascular and nervous structures, the eye being included with the nervous system.

2. Take the necessary time at the first interview or immediately thereafter to impress upon the patient that freedom from symptoms does not mean freedom from disease, and that a negative blood test is without arbitrary significance in the matter of cure. The same statement should be driven home regarding the spinal test and the fact that physical signs are sometimes the only evidences of serious symptomatic progress.

3. Subsequent re-examination should be maintained at a high standard as in the case of the base-line examination, and the temptation to give the patient a casual examination and to dismiss him on the basis of a negative Wassermann and a good general appearance must be constantly and determinedly resisted.

4. Every effort should be made to have the re-examinations carried through by the maker of the first or base-line examination. The increased thoroughness with which this can be carried out is a justification for sending patients with early syphilis to a consultation center for base-line study and recommendations if the physician in charge of the case feels himself in the least hampered by facilities or otherwise, in his work-up of the case. There is a nontransferability about the medical appraisal of a given human being which deserves consideration in reappraising any individual with respect to the status of the syphilitic infection. No written record can quite take the place of knowing and examining the patient himself.

Granted these preliminaries, the periodic re-examination of the patient with syphilis, whether the infection be early or late, should include:

1. The physical examination of the chest with a special ear to the aortic second sound ("tambour quality"), aortic systolic murmur, and cardiac and presternal dullness. The abdomen should be examined for palpable liver and spleen. Blood pressure should be taken in both arms.

2. Search should be made of the skin, scalp, mucous membranes, palms and soles, anus and genitalia, bones, and joints.

3. A history should be obtained which stresses cardiovascular and neurologic symptoms and warnings, and emphasizes infectious recurrence: dyspnea, precordial stress, pain on exertion, hoarseness; headaches, paresthesias, excessive nervousness, loss of memory, "nervous

breakdown," impotence, bladder retention, shooting and spot-like (?) pains, nocturnal ataxia, visual defects and impairment of hearing; sore mouth, cankers, herpes, chafes, "piles."

4. Hemoglobin, blood pressure, and urine should be examined.

5. Serologic tests on the blood including, in American practice, a Kolmer-Wassermann and at least a Kahn test.

6. In an early case, if possible, a provocative procedure. Weak positives should be checked in this way.

7. A neurologic examination with emphasis on pupils, lower cord reflexes and sensory changes, including vibration sense, muscle-joint sense (motion and position), differentiation of pain and touch.

8. The fundus, fields, visual acuity, reflexes, and muscle control of the eye.

9. A spinal fluid examination unless there have been two previous negative examinations separated by an interval of a year or more since the suspension of treatment.

DIAGNOSIS AND TREATMENT IN SPECIAL ASPECTS OF SYPHILIS SPECIAL DIAGNOSIS OF EARLY SYPHILIS

Diagnosis of the Chancre.—The past 20 years have seen a striking and critical shift of emphasis in the diagnosis of the onset of syphilis. Nineteenth century syphilology, lacking our present mechanism of tests and our knowledge of the organism, was obliged to depend wholly upon clinical criteria for the diagnosis of the chancre and accepted expectancy and observation as unavoidable and in fact desirable elements in the detection of the disease. Twentieth century syphilology, on the other hand, has relegated clinical signs and history to the status of "suspicion-arousers" and has largely placed the final diagnostic emphasis upon evidence obtained in the laboratory. Modern comprehension of the disease has, moreover, brought out clearly the tremendous importance of the earliest days in the life history of the chancre—that period in which the organisms are most abundant in the inoculation site but the blood serologic tests are still negative. These few days, which Pusey has well called "the golden opportunity" of the disease, are now the vital moment in the public health and in the individual situation. If the diagnosis can be made within this period of serologic negativity, the outlook for lasting arrest, for enduring noninfectiousness, is perhaps 35 per cent better than if dilatory tactics or the patient's ignorance results in later diagnosis. It is, the writer believes, impossible to overemphasize the fact that the lists of clinical criteria and the nineteenth century practice of waiting for the development of secondaries before instituting treatment are the two chief handicaps to the conquest of syphilis at the present day. The physician, therefore, who wishes to give his patients the best that modern knowledge can afford will make every effort to reach a conclusive diagnosis through the dark field, in the way previously described. He will attach little or no importance to this or that item in clinical appearance which may seem to speak against the possibility of syphilis; and he will fall back upon the positive blood Wassermann reaction as evidence only when every other diagnostic resort has failed. It is impossible to overemphasize the fact that every genital lesion, at least in a sexually exposed person, is potentially a chancre until it is proved to be otherwise. The mimicry of every type of genital lesion, from the scabetic burrow on the penile shaft to the shallow ulcers of

Vincent's and *ulcus acutum vulvae*, by the primary lesion of syphilis is well recognized by every experienced syphilologist.

Confusion of Chancre and Chancroid.—Chancroid is the particular pitfall of the large majority of practitioners. The war showed very clearly that American practitioners of that day were notably deficient in their ability to differentiate chancre from chancroid.¹³⁵ This is perhaps less a criticism of the profession than a tribute to the very great importance of double infection in which a Ducrey organism produces a lesion which simply acts as a mask over the surface of what is in reality the onset of syphilis. The practicing physician who deals with early syphilis should realize that 65 per cent of genital lesions are syphilitic; that only 14 per cent of those which are negative to the dark field are subsequently shown to be syphilitic by the outcome of repeated Wassermann tests; that the risk of being in error in making a diagnosis of chancroid is probably not less than one chance in three and more often one chance in two. It cannot be overemphasized that syphilis will constantly escape unrecognized at its very onset, until the medical profession adopts the principle that a final diagnosis of chancroid, irrespective of whether the lesion is treated or not, cannot be made for four months following the first appearance of the sore. This statement is more fully explained in connection with serologic follow-up.

Chancre Masked by Gonorrhea.—Another fact too often overlooked in ordinary practice is the concealment of the onset of syphilis by a coincident or preceding gonorrhea. Approximately 20 per cent of patients recognized as syphilitic in later life can give only a history of gonorrhea. This means essentially that the onset of the disease was masked by the Neisserian infection and took the form presumably either of an inconspicuous chancre elsewhere on the genitalia or of a meatal or intra-urethral primary lesion which passed unrecognized beneath the discharge and inflammatory symptoms of the less serious disease. It follows, therefore, that every patient with gonorrhea should be subjected to the same rule as the patient with chancroid, and that no final diagnosis of gonorrhea uncomplicated with respect to syphilis should be made within four months of the onset of the Neisserian infection.

"No History of Syphilis".—Emphasis should also be placed on the fact, particularly because of the importance too often attached to it in later life, that the history of a syphilitic infection, as given by the patient, may be entirely unreliable. Twenty per cent of men and 60 per cent of women can give no history of a primary lesion.

Clinical Suspicion-Arousers.—Granted, then, that the diagnosis of early syphilis must rest upon laboratory rather than upon clinical criteria, the suspicion-arousing quality of clinical signs may none the less be pointed out. Of the ten characteristics of the chancre emphasized by the older clinicians, four still retain their importance as strong presumptive evidence in favor of the syphilitic character of a genital or extragenital lesion. These are, first the relatively *long incubation period* following exposure. Most banal lesions develop within the first four days, most chancres between the tenth and the twenty-fourth day after exposure. This rule, however, fails before the possibility of a mixed lesion, in which a banal condition such as chancroid or herpes appears within the first four or five days, while a subsequent and underlying syphilitic infection does not begin to produce recognizable signs until the second or third week. The second clinical characteristic of present-day

significance is the *indolent and prolonged course* of the syphilitic primary lesion. In other words, refusal to heal and a persistence of more than seven to ten days should arouse suspicion of syphilitic origin. The third suspicion-arousing item is the presence of *induration* in the primary lesion of syphilis. While induration may be produced especially by ill-advised attempts at treatment, it is none the less true that firmness or hardness of the base of the lesion has high value in suggesting the possibility of syphilis. The fourth surviving criterion and in many respects the most important of the group is the presence of a *satellite lymphadenopathy* or bubo in the lymphatic drainage area of the suspected sore. Adenopathy is by no means a necessary accompaniment of a chancre and as high as 30 per cent of primary lesions lack it entirely. None the less, the appearance by the seventh day of a painless, indolent and discrete lymphatic enlargement, whether unilateral or bilateral, points very distinctly toward a syphilitic primary lesion. Even in the differentiation of chancreoid this applies and justifies the routine search of adjacent lymph nodes if they are enlarged and palpable, for the *Spirochaeta pallida*. Such items as the unilateral in contrast to the bilateral character of the adenopathy with genital lesions should no longer be allowed to carry any real weight. Incubation, indolence, induration and satellite adenopathy are, then, the four characteristics of a potential primary lesion on which it is still possible to lean for clinical support and suspicion-arousing value in the diagnosis of the chancre.

The foregoing statement applies with special emphasis to the extragenital primary lesion. If all supposedly nonspecific infections of the fingers, supposed herpes of the lip, supposed Vincent's angina or diphtheria of one tonsil, or suspected tumors and cancers of the lip and nipples in young persons could be suspected of being syphilitic, many of the most tragic cases of extragenital infection would be nipped in the bud. The shortcomings of physicians in the recognition of their own accidental infections are almost unbelievable. Every lesion of the skin and mucous or serous surfaces which has refused to heal within ten days, which is indurated and which presents a well-marked satellite adenopathy, deserves investigation for the possibility of syphilis. The practice of applying any form of treatment to a genital sore before the performance of such an examination is reprehensible and cannot be condoned. According to various figures, the application of such local treatment reduces the possibility of a positive dark field from 81 per cent to 28.5 per cent. The writer's own experience (reported with McFarland¹³⁶) however is somewhat more favorable in that 74 per cent of 17 treated chancres yielded positive dark fields. In order to obtain serum enough to be collected in a capillary tube and sent to a laboratory for dark field study, constriction and congestion of the site of the primary lesion by a rubber band tied about the penis has already been mentioned. If no satisfactory dark field can be obtained from the lesion directly, a specialist should, if possible, be called to assist in the aspiration of the base of the lesion or the adjacent lymph nodes. It may be reiterated that dependence on a blood serologic test to identify a syphilitic infection at this stage is only justifiable, if at all, when absolutely no assistance for an earlier diagnosis can be obtained. The situation which arises when a strongly suspicious lesion proves to be associated with a negative blood Wassermann reaction is one of the most difficult in modern syphilologic practice. The impulse is almost irresistible in

some cases to start treatment on the clinical appearances alone. This urge was rendered the stronger in the days when abortive cure was considered to be feasible and to constitute a short and easy alternative to the more thorough-going treatment of a Wassermann-positive, fully developed infection. At times even the expert, failing to secure a positive dark field on repeated examination of lesion and lymph nodes, wavers between the decision to treat on physical characteristics and the advisability of waiting until the blood Wassermann reaction confirms or negates the diagnosis. In situations of this sort, the course to be followed appeals to the writer thus. There should be no attempt at a provocative procedure or a therapeutic test as such. To leave the patient at the close of a provocative test or one or two treatments which have failed to produce satisfactory involution, is to leave him in really desperate danger from relapse, should the condition actually be syphilis. If it seems advisable to begin treatment without a fully substantiated laboratory diagnosis, and on the basis of clinical criteria alone, the patient should have the situation frankly explained to him. He should be told that the drawback of waiting for positive diagnosis consists in the loss of nearly one-third of his chances of "cure." On the other hand, if he allows the institution of treatment before the diagnosis has actually been made, he must, from the moment that the first injection is given, consider himself as having a syphilitic infection and pursue the treatment of it in full detail to the very last ditch. Only in this way can he escape the dangerous consequences of insufficient treatment. On the other hand, he obtains, in compensation, the one-third greater possibility of supposed radical cure. The requirements of a modern scheme of treatment for early syphilis should be explained to him so that he may know in advance exactly what is expected of him. If he accepts the alternative and wishes treatment begun on the clinical appearance of the lesion, the physician must himself assume the attitude of mind that he is now dealing with a proven infection and act precisely as if the dark field had been positive. It will be seen later that this implies exactly the same amount of treatment (to a maximum, not a minimum) which is desirable for the fully developed secondary infection. The patient, then, does not secure any shortening of the amount of treatment required through his willingness to assume the lesion to be syphilitic, but he does, we believe, secure a 35 per cent greater possibility of cure by accepting the supposition that the lesion is syphilitic.

Should it be decided by the patient and physician that systematic treatment shall not be begun until a positive diagnosis is secured by the blood test, it is perfectly proper, after every effort has been made to obtain a positive dark field by the use of saline compresses, aspiration and so forth, to begin the local treatment of the sore by hot bichloride solution soaking (1:2000), the cautery or whatever other measure may be indicated from the local standpoint alone.

If the blood Wassermann reaction obtained on a patient with an early primary lesion is negative but the dark field positive, treatment should be begun at once; but the blood Wassermann reaction should be repeated between the first and second treatments to make sure that in the interval, and as a result of the provocative effect of the first treatment, it has not become positive. Sero-negative primary cases which become positive following the first treatment and then thereafter negative again, should be regarded as essentially sero-positive primary cases

rather than as completely sero-negative. This places the really significant sero-negative phase of primary syphilis from the therapeutic standpoint between the third and the seventh day of the life of the chancre, for later lesions are very apt to become positive on the blood with the first treatment.

The tremendous importance of time in all these considerations and manipulations cannot be overemphasized. The patient with a suspected primary lesion of syphilis is really in a state of desperate emergency rather than the conventional one of leisurely observation. The patient in such a situation should have access to the physician at any hour of the day and the telegraph and long distance telephone may properly be used in securing him the quickest possible service. If a positive blood Wassermann reaction is returned while the lesion is under observation, it is, however, allowable to postpone the beginning of treatment until a repetition can be had and reported on by telegraph. Partial and weak positive Wassermann reactions have been reported on lesions which subsequently proved to be nonsyphilitic in character.

The serologic follow-up of a patient with a suspected lesion is a matter of the greatest importance. As previously stated, it is impossible in at least 14 per cent of syphilitic genital lesions to make a diagnosis by dark field methods and the maximum efficiency of the positive Wassermann reaction is not reached before the fifth or sixth week. This gap between the maximum effectiveness of the two diagnostic procedures must be filled by repetitions of the blood Wassermann reaction at least at weekly intervals until the end of the second month, regardless of the original characteristics of the lesion. If a positive has not been obtained by this time, the test may be repeated at the end of the third and at the end of the fourth month to cover tardily developing positives. While it is desirable, of course, to examine the patient in connection with these test repetitions, examination should under no circumstances be allowed to take the place of the Wassermann test itself. It is entirely possible for a patient to go on to a syphilitic infection without the development of a single recognizable external sign. The only way, therefore, to forestall the large margin of possibility that a patient has syphilis in spite of an atypical onset is to insist routinely on this so-called Wassermann follow-up on all patients with genital lesions following exposure and all patients with gonorrhea.

Diagnosis of Secondary Syphilis.—In the description of the secondary syphilitic eruptions, sufficient emphasis has perhaps been placed upon the fundamental necessities for successful diagnosis. Complete examination with attention to the stripped torso, the mucous membranes, palms, soles, anus and genitalia, including the posterior surface of the scrotum, all to be conducted in a good light and with provision for distant inspection, is the minimum requirement. The blood serologic tests by current methods have now reached such a point of sensitivity that they may properly be relied on for confirmatory judgment. In other words, it is safer to consider an eruption accompanied by a positive blood Wassermann reaction as syphilitic and to treat the patient for it as such, than it is to refuse to believe the positive Wassermann and to consider the eruption, though undiagnosed, a merely banal affair. It is equally proper to consider that an eruption which is sero-negative is not a secondary syphilid. In any case in which the ensemble of the clinical features and the history seem to speak strongly for a

diagnosis of syphilis yet the blood serologic tests are negative, dermatologic consultant advice should be sought. The patient has already lost the advantage of his sero-negative primary phase and the few days' additional time in definitely settling the question as to whether or not he has syphilis can certainly do no harm and may save him enormous expense, great mental distress and many subsequent medical misinterpretations.

It cannot be too often reiterated that certain constitutional syndromes, if constantly investigated with the possibility of syphilis in mind, would yield a large harvest of identified and treated early syphilis, to the glory of preventive medicine. Particular emphasis should be laid on the combination of headache and sore throat of more than a week's persistence; the possibility that severe and particularly one-sided tonsillitis or diphtheria may be syphilis even though accompanied by high fever and great prostration; the possibility that rheumatoid symptoms may be a phase of secondary syphilis; that anemia, anorexia, cough and loss of weight in young women may be syphilis; that headache, asthenia and chlorosis may be syphilis—these combinations and permutations, it must be insisted, should constantly be borne in mind as masks for the onset of an early syphilitic infection.

The aim of all modern treatment for early syphilis is dual in nature; first, to sterilize the individual completely by killing all spirochetes while they are accessible; and, second, to protect the patient against the dangers of relapse in case complete sterilization fails. The therapist should approach the treatment of a patient with early syphilis without a thought to his future except as it is involved in the absolute extermination of all organisms and the radical cure of the disease within such limitations as may be prescribed by a restricted tolerance. Nothing, on the whole, can be more unwise than for the physician confronting his early case to "pull his punch" by any reflections on the proportion of failures and the insufficiencies and gaps in even our modern knowledge.

Logical Methods of Accomplishing the Aim.—If the embattled syphilologist is permitted one more lapse into the vernacular of the ring, it is to impress the fact that syphilis is worn out rather than knocked out by treatment in a sufficiently large proportion of cases to justify a prolonged, determined rather than a short, hyperintensive method of treatment. The last spirochete is probably reached by the body, rather than by the circulating drugs. Hence, since the infection is general from the start and worn out rather than knocked out; and since unprotected relapse is especially dangerous because of an acquired allergic state, the following rules should apply.

Rule 1. Discard any idea of reducing or shortening treatment because the patient has been seen early in the course of his disease or because the blood serologic tests were negative at the start. The concept of abortive cure for a long time had its stronghold in German practice. The most significant commentary upon changing opinion, even in Germany, is the fact that in his recent radio broadcast to the entire German Empire, the premier syphilologist of that nation, Geheimrat Jadasohn, advocated, not the administration of a single "abortive cure" but of one, two, three or even more successive abortive cures in any and every early case.

Rule 2. Treat, therefore, to a maximum determined by large experience and not by individual "I-had-a-case" methods, selecting for

the purpose systems of treatment which are known from the experience of large clinics and investigators to give the highest proportion of lasting "curative results" in fully developed secondary syphilis.

Rule 3. Mass the treatment well to the fore, giving the maximum tolerated amount in the first week, in the first three weeks, the first three months rather than later, in order to reach the organisms while they are accessible in the blood stream, and before they have encapsulated themselves by the fibrotic changes which their presence induces. All too frequently, a desultory and easy-going beginning to treatment ends in a panic rush of over-treatment and reaction as an infection which has become Wassermann-fast gradually discloses itself.

Rule 4. Use moderate but not small doses, for huge doses endanger the patient's tolerance too early in the prolonged course which is necessary for best results, and invite dangerous complications. Continental practice, which is essentially low-dosage in character, is evidently, from its results in the general control of syphilis, quite adequate to the large majority of cases when properly employed.

Rule 5. Administer the arsphenamine phase and the heavy metal phase of treatment *simultaneously* or with overlap, and not in alternation. Only in this way is it possible to avoid the very serious dangers of relapse contingent upon the failure to develop tissue resistance and to maintain a constant inhibitory and destructive fire upon the organism during the period of greatest susceptibility to relapse, namely, the first two years of the disease.

Rule 6. Allow no rest intervals during which the patient is completely released from treatment, even though only for as long as a week. This rule should apply to at least the first 18 months of the disease.

Rule 7. Do not suspend treatment until the patient has been clinically and serologically negative, including a negative spinal fluid, for at least one year.

Rule 8. Even though every conceivable advantage has been available from the very start, never discharge a patient as cured. Watch the vascular and nervous systems throughout life.

Practical Standards for Rule 2 (Maximum Treatment).—In the past several years, two methods have been used for determining the optimum amount of treatment for the patient with early syphilis. The first of these has consisted in the reëxamination of patients receiving varying amounts of treatment at various intervals following the onset of their infection and the second has consisted in the study of clinical and especially of infectious relapse. The studies based on reëxamination from American sources may be briefly summarized. The writer, working with Becker¹³⁷ upon Mayo Clinic material consisting of 116 cases of early syphilis, showed that the incidence of relapse of any kind is proportional to the number of arsphenamine injections and that relapse was less frequent (20 to 25 per cent as compared with 30 to 35 per cent) when treatment is pushed within the first seven to ten days. Moore and Kemp,¹³⁸ who have collected what is without question the finest series of early cases in existence from the service of the Johns Hopkins Hospital, have also shown that relapse is proportional to the number of arsphenamine injections which the patient receives. Their figures deserve quotation. In sero-negative early syphilis receiving 1 to 8 injections, 76 per cent relapsed. When 6 to 12 arsphenamine injections had been given, only 54 per cent relapsed. After 13 to 20 injec-

tions, 14 per cent relapsed; and after 21 to 40 injections, there was no relapse. In patients with sero-positive primary lesions, 90 per cent of those receiving 1 to 8 injections relapsed, 53 per cent of those receiving 6 to 12 injections relapsed, 50 per cent of those receiving 13 to 20 injections, and 40 per cent of those receiving 21 to 40 injections. In florid eruptive secondary syphilis, 90 per cent of those receiving 1 to 8 injections relapsed, 67 per cent of those receiving 6 to 12 injections relapsed, while the proportion of relapses decreased to 48 per cent in the groups having 13 to 20 injections and to 23 per cent in the groups having 21 to 40 injections. Moore and Kemp¹³⁸ showed that relapse in the blood Wassermann reaction is ten times more frequent in patients who have been on a rest or lapse from treatment between the first and second or the second and third arsphenamine courses, than in patients who have been treated continuously. They showed furthermore that clinical recurrences endangering life and efficiency occur in almost half the patients receiving 8 or fewer injections of "606." (Imagine, therefore, the larger proportion with "914.") One-third of those patients who received one to two courses with mercury, one-fourth of those receiving three treatment courses, and less than one thirty-third (3 per cent) of those receiving four or more courses plus mercury, subsequently suffered clinical recurrence.

In a recent report on five years' use of bismuth arsphenamine sulphate in 54 early cases of syphilis, Miller, Beerman and the writer¹³⁹ succeeded in showing that relapse occurs in 9.1 per cent of continuously treated and 14.3 per cent of rest interval cases. They showed also that even with comparatively much less treatment, the continuously treated cases were less likely to relapse. It was possible also in this study to bring evidence to bear to the effect that two injections a week led to slightly less relapse than one injection per week.

Treatment Requirements in Early Syphilis as Evidenced by the Control of Infectiousness.—Within the past year, studies of infectious relapse have appeared from which it is possible to deduce important conclusions regarding adequate treatment for early syphilis. The literature of this subject is fully reviewed in a study by Stokes, Besancon and Schoeh¹⁴⁰ from the material of the Syphilis Clinic at the University of Pennsylvania, and important general conclusions based on the largest existing material were presented before the International Congress of Dermatology and Syphilology at Copenhagen in August, 1930, by a co-operative group working under grant from the Committee on Research in Syphilis for the American League of Nations investigation.¹⁴¹ Inasmuch as infectious relapse has great intrinsic public health importance for the spread of the disease and likewise serves as an excellent index of the results of treatment in early syphilis, these conclusions are here summarized. Relapse in early syphilis is controlled overwhelmingly by the arsphenamine factor in treatment. Thus, 35 per cent of relapsing patients had less than five doses of an arsphenamine, and adopting less than 20 injections of an arsphenamine as the median, 87 per cent of relapses fall within the group receiving less than this amount of treatment. In fact, 81 per cent of relapsing patients had less than 15 arsphenamine injections. Considering 20 arsphenamine injections and 20 injections of a heavy metal (either mercury or bismuth) as a median standard, five times as much relapse occurs in patients receiving little arsphenamine and little heavy metal as among those receiving much

arsphenamine and much heavy metal. As between patients receiving much arsenic and much heavy metal, and little arsenic and much heavy metal, those having the larger proportion of arsenical treatment have the less relapse (2.7 per cent as compared with 5.3 per cent, or nearly double). This, then, is a justification for insistence on arsphenamine treatment to prevent mucocutaneous relapse in early syphilis. The apparent relatively greater effectiveness of arsphenamine and bismuth as compared with arsphenamine and mercury (3.6 per cent as against 9.6 per cent) in preventing relapse has already been noted. The analysis of cases receiving little arsphenamine and little heavy metal gives some index of the amount of arsphenamine that may be expected to be effective in preventing mucocutaneous relapse. Of those cases which receive one to four doses of arsphenamine, 64 per cent relapse; while of those who received as much as five to nine injections, 14 per cent relapsed. In other words, the critical point for a large proportion of patients with early syphilis with respect to the prevention of potentially infectious relapse lies between the fifth and the ninth arsphenamine injections. The public health implication of this conclusion is obvious. The analysis of the group receiving little arsphenamine and much heavy metal reveals that of 22 cases who received from one to four doses of an arsenical with 20 or more injections of heavy metal, 45 per cent relapsed; while of 81 patients who received five to nine injections of arsphenamine with 20 or more doses of heavy metal, only 9 per cent relapsed. In other words, arsphenamine is much the most important element among the several involved in early treatment, in the prevention of relapse; and relapse, even with identical heavy metal treatment in the two groups, is five times as common in the patients who receive only one to four doses of an arsenical as in those who receive from five to nine doses. Moore and Kemp^{138, 140} found in their series that 85 to 88 per cent of relapsing patients received less than 13 arsphenamine injections with mercurial or bismuth treatment. In the writer's own clinic 119 patients receiving both arsphenamine and mercury or bismuth, who had lapsed three months or more, showed the following proportions of relapse.¹⁴⁰ In those who had received an average of 8.6 injections of arsphenamine and 4.4 injections of a heavy metal, 13 per cent relapsed; while of those receiving an average of 28.8 injections of arsphenamine and 28.2 injections of mercury or bismuth none relapsed. It appears, therefore, that responsibility for relapse in early syphilis rests directly upon inadequate treatment and particularly upon an insufficient arsphenamine phase. Not less than 20 injections of an arsphenamine—and more, if possible, preferably in one or two courses—and an equivalent amount of heavy metal without rest intervals, should be given in an early case to control infectiousness. It may not be out of place here to quote the results of an effort to trace the responsibility for relapse as between physician and patient. Both parties seem to be equally at fault. The physician errs in not educating his patient, in giving too little treatment, and especially in relying on a few injections of neoarsphenamine unsupported by effective heavy metal treatment. He also cannot, or does not, utilize the full possibilities of follow-up, either personally or through the state. It is particularly important that the physician should not allow the patient to get the impression that a negative blood Wassermann reaction has any significance with respect to his cure. The first negative Wassermann reaction, especially when the patient is thus discharged to observa-

tion, is the landmark for lapse in many cases, and the occasion for a mistaken relaxation in requirements and vigilance by the physician. It cannot be overemphasized that the treatment of early syphilis, to be effective, should be conducted without direct reference to the outcome of blood serologic tests. Even though they are repeatedly negative, treatment should be continued in accordance with the empirical standard above outlined, until the patient has received the amount of arsphenamine and heavy metal which the studies quoted indicate is the optimum for the "cure" of the disease.

Standard Systems of Treatment for Use in Early Syphilis.—It would seem with the statistical material above elaborated, that it should be possible to define a standard treatment of early syphilis which would be satisfactory to practically all observers. This, unfortunately, is not the case. The differences of opinion as to the indications and contraindications for the simultaneous or alternate use of heavy metals and arsenic, the insertion of rest periods, the use of serologic criteria or progress and cure, give endless ground for slight or important differences of opinion. Moreover, the facts just cited are the result of comparatively recent studies and an attempt to define a standard treatment procedure using them as a basis will not be forthcoming in less than another year or two. There can be little question that almost any system of treatment reasonably attentive to the above considerations should produce 60 to 65 per cent of "cures" or permanent arrests. But for every 5 per cent gained above this point, certain crucial details not as yet completely proven will probably be vitally important. It is, therefore, only possible to say at this time that alternate courses of an arsphenamine with mercury or with bismuth, the arsphenamine courses ranging from four to eight injections in number and the bismuth or mercury injections from four to ten in number, are quite widely used. Four such arsphenamine courses and six of the longer heavy metal courses are quite commonly employed. The individual dosage of the arsphenamine and heavy metal in this country tends to be rather high, and Schamberg⁶⁷ in particular has protested against this distinctly American tendency to high dosage which he feels is responsible for much injury to the liver, skin and kidneys. On the other hand, such dosage systems, provided the individual courses are not too prolonged, have been successfully used for more than a decade by several of the larger services in this country. Drawing on the very large experience of the British Ministry of Health, Colonel Harrison, who is probably the first English-speaking proponent of the simultaneous use of the arsphenamines and heavy metals,¹⁴¹ gives only nine injections of neoarsphenamine in bursts or spurts of two or three injections each with ten injections of a bismuth salt, the entire course covering 120 days. The unit courses thus described total 6.6 Gm. of neoarsphenamine and 4 Gm. (60 Gr.) of bismuth. In its discussion of the management of syphilis in general practice, the United States Public Health Service, through Moore as spokesman,¹⁴² voiced the opinion of six American syphilologists in favor of a "cure" of 32 arsphenamine injections and 38 injections of bismuth salicylate, the arsphenamine phase being divided into an intensive beginning of three injections in the first ten days followed by five additional weekly injections and then by four weeks of bismuth without arsphenamine. Following the bismuth interlude, the arsphenamine and heavy metal phases alternate, six injections of arsphenamine being followed by

six, eight or ten doses of bismuth, to the completion of the course. The writer personally employs almost precisely this course in treating early syphilis with arsphenamine, except for the use of overlap and consequently longer bismuth courses. In the writer's technic bismuth and arsphenamine are given simultaneously, beginning with the fourth or fifth injection. The arsphenamine rest period is given in the middle of the bismuth course and the later three or four injections of the next arsphenamine course. More recently the writer has been inclined to reduce the arsphenamine dosage from 0.4 and 0.6 Gm. to 0.3 and 0.4 Gm., and to give bismuth simultaneously throughout a more prolonged course of 16 to 20 injections absolutely without a rest period. Four to six weeks of rest from the arsphenamine phase is then allowed while the patient continues to take bismuth. A second arsphenamine course then begins in which the patient is allowed his rest period from bismuth, and ends with 20 to 30 additional bismuth injections, the last five or six of which overlap the end of the second arsphenamine course. The increased intensity of this system and its longer duration are compensated by the more moderate dosage of the individual drug and by protection against toxic effect through the use of calcium intravenously before the arsphenamine injections and occasionally of glucose likewise. (Colonel Harrison has recently discarded the practice of giving the patient a large dose of glucose by mouth and of mixing the neoarsphenamine in 20 cc. of 40 per cent glucose solution as a protection to the liver.¹⁴³)

Inasmuch as the large majority of practitioners use neoarsphenamine, the following technic, approximating that used by Schamberg for a number of years, may be suggested. Neoarsphenamine in doses of 0.3 to 0.45 Gm. may be given intravenously on the same day as the intramuscular injection of bismuth, the interval between injections ranging from three days early in the course to five or seven days later in the course, with the total series of injections in the first course approximating 20. A rest period is then allowed, covered by bismuth or not as the individual therapist may prefer, and treatment is again resumed with the simultaneous administration of small doses of neoarsphenamine and moderate doses of bismuth intramuscularly. In such a course the writer endeavors to approximate 40 arsphenamine injections as a total and extend the treatment to a full period of 16 or 18 months by two tapering-off courses of bismuth or one of bismuth and one of mercury salicylate or inunctions.

If bismuth arsphenamine sulphonate is employed for the treatment of early syphilis, it is urged that two injections be given each week for a single course of 40 injections absolutely without a rest period. Disappointment and neurorecurrence are much more apt to follow any break in the continuous system with this drug. The tapering-off treatment with bismuth and mercury intramuscularly may then be given as in the neoarsphenamine system.

The persistence of a positive blood Wassermann reaction in early syphilis seems to be largely dependent upon irregularity and lapses in treatment and the introduction of unwarranted rest intervals.¹⁴⁴ Particularly are rest periods dangerous in the first three months of treatment. If the blood Wassermann reaction is positive beyond the twelfth week on any of the systems of treatment above described, treatment should be continued according to routine and absolutely without rest intervals until the end of the sixth month. The spinal fluid should then

be examined to determine the possibility of a neurosyphilis underlying the fixed positive blood test. Patients who show a preponderantly negative Wassermann reaction throughout the year and a half of treatment but who have, even occasionally, shown a tendency to slight positiveness, are to be regarded as under suspicion; and observation of the nervous system and cardiovascular system should be particularly close during the ensuing five to ten years.

Observation of the patient with early syphilis once treatment is discontinued, should be more frequent than is usually the case. Inasmuch as the effort is to detect any signs of relapse, a physical examination with a blood serologic test should be carried through at least every two or three months during the first year of probation, and the patient should be instructed as to what symptoms and lesions to watch for as evidence of recurrence.

RELAPSE AND RECURRENCE

The foregoing discussion of treatment in early syphilis has brought out the preventive measures which should make the period between an acute onset and latency or cure, free from manifestations of relapse so far as the skin and mucous membranes are concerned. It seems probable that the same principles will apply to the relapsing blood Wassermann reaction whose incidence is very much the same as that of cutaneous relapse. Even under the best of conditions, however, some cases will prove unresponsive, and familiarity with relapse in its various forms therefore becomes essential in the management of all and particularly the early phases of syphilis.

Forms of Relapse.—The physician dealing with early syphilis should be on the lookout for any or several of the following forms of relapse in any given case.

1. Relapse or reappearance of the chancre.
2. Delayed or repressed secondaries, which may appear after as much as three years' absence of symptoms in patients treated during what was apparently still the primary stage of the disease.
3. Complete recurrence of a secondary eruption and even of a primary lesion and secondaries, the latter in mild or aggravated form, following inadequate treatment.
4. Appearance of isolated recurrences, especially of buccal and anogenital lesions, with the patient apparently in good health and even with a negative blood Wassermann reaction, as late as six years after the onset of the infection. Such mucosal recurrences have been reported as late as 24 years after infection, but the overwhelming proportion (94 per cent) occurs in the first two years after treatment ceases, and 85 per cent in the first two years of the disease.
5. Neurorecurrence, either asymptomatic or detected only by spinal fluid examination; or symptomatic, as in the case of second, seventh and eighth nerve involvement especially, the blood serologic tests being either positive or negative.
6. Development of cardiac and aortic lesions in apparently arrested or "cured" cases. The blood serologic tests under such circumstances may be either positive or negative.
7. Development of bone and visceral lesions, recurrent anemias and asthenia, usually associated with relapsing blood Wassermann reactions.
8. Asymptomatic blood Wassermann relapse, either under treatment

or in rest intervals, or following provocative procedure. This might also include the fixed positive and the fluctuating positive as well as the relapse after a period of complete negativity.

9. Birth of a syphilitic child to an apparently healthy and serologically negative mother who has had syphilis.

10. Infection of the sex partner with syphilis in the absence of detectable clinical or serologic relapse in the patient.

11. Precocious tertiarism: the onset of late lesions months or years before their time as a result of allergy and reduced resistance usually from improper treatment, especially with arsphenamine.

12. Iritis, occurring in about 2 per cent of syphilitic patients usually after the first year.

13. Hepatorecurrence and splenomegaly. Enlarged livers are found in 10 per cent of routinely examined latent cases, the enlargement coming on presumably during the late secondary period. Enlargement of the spleen is much less common (0.8 per cent) and both liver and spleen are palpable in 5 per cent. Signs of jaundice and of liver tenderness accompanying the enlargement are part of the picture of hepatorecurrence in an early inadequately treated syphilis.

Because of their very great importance from the public health standpoint, mucocutaneous recurrences should be more familiar to the practicing physician. The patient whose treatment is begun in the sero-negative primary stage is more prone to mucocutaneous relapse than is either the sero-positive primary patient or the florid secondary patient. Thus it would seem that the gradually developing resistance of the patient to his infection cuts the proportion of relapses from 10 per cent in the sero-negative primary stage to 8.55 per cent in the sero-positive and 4.16 per cent after generalized secondaries have appeared. The recent study of the statistical material of five American clinics¹³⁴ indicates quite clearly that there is a distinct mucocutaneous relapsing type of patient who tends to develop delayed secondaries appearing after the first year of the disease and who relapses in 22.31 per cent of cases or more than twice as often as even the sero-negative primary cases. Such patients are five times as prone to relapses in the mucous membranes as are patients who have developed secondary lesions. The tendency to use this as an argument for allowing patients to progress to the stage of secondary eruption before they are placed under treatment must be vigorously combated. The mere fact that developing a generalized or systemic reaction to the disease slightly reduces the incidence of infectious relapse does not for a moment compensate for the enormous loss in prospect of ultimate cure and for the practically absolute control of infectiousness which can be exercised through adequate prolonged and continuous modern treatment with the arsphenamines and a heavy metal, when begun in time.

The mucocutaneous relapse¹⁴⁵ occurs upon the genitalia in 31.4 per cent of cases and elsewhere in 68 per cent; 62 per cent of them are potentially infectious and 74 per cent of the genital lesions occur on the penis and vulva, where they are best situated for the perpetuation of the disease. The study of this problem conducted in the writer's own clinic indicated that the anogenital region is the exclusive site of relapse lesions in 41 per cent of patients and the mouth alone in 17.6 per cent. At the time of examination, nearly 50 per cent of the anogenital lesions were infectious and positive dark field examinations were ob-

tained on 78 per cent of the cases examined by this method. The serologic tests tend to be positive in mucocutaneous and infectious relapse, the proportion (96.5 per cent) being very close to the incidence of the positive Wassermann in secondary syphilis itself. Accordingly a considerable amount of assistance in the detection of relapse may be obtained by frequent repetition of the blood Wassermann.

Serologic Relapse.—Among the 5,952 cases of early syphilis studied by the coöperative clinical group of American syphilologists previously mentioned, serologic relapse was found to occur without mucocutaneous lesions in 4.37 per cent as compared with 6.05 per cent of mucocutaneous relapse. Moore and Kemp, it will be recalled, showed that serologic relapse is ten times more frequent in patients who have been on a rest or lapse from treatment between the first and second or the second and third arsphenamine courses, than in patients who have been treated continuously. The problem of deciding whether a positive interspersed between several negatives in early syphilis is a bona fide serologic relapse or a laboratory error, is sometimes very difficult of determination and calls for the use of the provocative procedure as well as more frequent repetitions of the test. In one such case under my observation, two brief lapses into positiveness seemed entirely without explanation except on the score of laboratory error. It was not until the liver enlarged sufficiently to be palpable below the costal margin, following the second unexpected positive test, that the sources of the trouble were established in the form of a subthreshold hepatitis. This patient has had extremely thorough treatment, but apparently belongs to the category of alcoholic recidivists. His liver promptly subsided on the resumption of intensive antisyphilitic treatment but a very definite provocative effect with an ascent to a maximum and a decline again to negative over a period of four weeks was observed as the intensive treatment was resumed. It is apparent, therefore, that even slight degrees of positiveness may have great significance in early syphilis and should never be taken lightly.

Neurorelapse in Early Syphilis.—This¹⁴⁵ may occur alone or in combination or sequence with other forms of clinical recurrence. The most recent American study is that of Moore *et al.*, who find the frequency of the complication to be 0.2 per cent. For example, a patient under the writer's observation sustained a hemiplegic neurorecurrence following a second outbreak of cutaneous secondaries. Neurorecurrence may, of course, be asymptomatic and detectable only on examination of the spinal fluid, though in such cases as this a blood serologic relapse usually gives warning of what has occurred. Serious neurorecurrences of the isolated vascular type involving the second, seventh and eighth nerves may develop even though a previous negative spinal fluid has seemed to indicate that the nervous system is free from involvement. Unfavorable progression of all these types of lesions may take place in spite of treatment and, in fact, they may come on in the very middle of a course of what seems to be effective treatment. In such cases, intraspinal and fever therapy must particularly be considered.

Reinfection.—Reinfection is here considered in conjunction with manifestations of relapse because thorough-going critical study of the problem seems to indicate, as was stated at the International Congress in 1930, that reinfection was indistinguishable from relapse and super-

infection. It is impossible here to go into a critique on the reinfection concept in the relation to the immunology of the disease, but the literature on the subject, together with characteristic observations, has been recently covered by Stokes, Schoch and Ireland.¹⁴⁶ A critical analysis of the elaborate criteria proposed by Bernard¹⁴⁷ for a determination of the validity of reinfection, of the less stringent criteria proposed for the very large series of cases examined by Halley and Wasserman,¹⁴⁸ and of the 40 reinfections studied in connection with the work of the five American coöperating clinics,¹³⁴ has indicated quite clearly that no reinfection thus far described can survive the cross-fire of the most critical schedule of criteria. The proportion which survives even moderate critical analysis is very small and one is inevitably forced to the conclusion that clinical reinfection in man is as yet an unestablished entity and that the term "second infection," which allows room for the superinfection possibility, should be used instead. Certainly, no critical examination of the existing information on the subject would allow a conscientious observer to use so-called reinfection as a proof of cure of the original infection.

Treatment of Early Relapse and Recurrence.—The treatment of the genuinely relapsing case is one of the discouraging problems of modern syphilotherapeutics. If the patient has not already had the benefit of the type of treatment above described for early syphilis, it should be administered and carried through with intensity and every precaution to protect against serious reaction or permanent damage. As in the management of the fixed positive serologic case, variation in the type of treatment, the use of "one more drug" may bring about striking and lasting results. Every one of the entire range of drugs thus far described in this presentation can be employed in the attempt to conquer permanently a relapsing tendency. Ultimately, however, one cannot but feel that the control of relapse is less in the treatment of consequences than in the **thorough-going attack on the infection at the outset**. No variety of drugs or methods used late can take the place of an effective use of an **arsphenamine** at the outset; very short or **no rest intervals** from treatment as a whole; **repeated courses**, or an attempt to carry the total arsphenamine series as near to 40 injections as possible; and **simultaneous use** of both arsphenamine and heavy metal with complete serologic and clinical control. Fever therapy may, of course, be tried; but its ability actually to induce relapse in some cases, at least of late cutaneous symptoms, does not seem to make the outlook, apart from disease of the nervous system, particularly encouraging.

SPECIAL DIAGNOSIS AND TREATMENT OF BENIGN LATE SYPHILIS

The remainder of this presentation of the subject of syphilis will deal with certain aspects of the special diagnosis and treatment of the later lesions of the disease. The intention is merely to bring out important principles in keeping with the preceding general discussion of the diagnosis and treatment of syphilis. For further detailed information reference should be had to other parts of this system of medicine which are intended to deal with syphilis in special structures.

Cutaneous and Osseous (Benign) Late Lesions.—Under the heading of the special diagnosis of benign late syphilis, cutaneous, osseous and certain miscellaneous lesions will be discussed. The term benign is used to indicate that under ordinary conditions, both in the course of the

disease and in its therapeutic management, the problems presented by the individual case rarely threaten life. This cannot, of course, be invariably true, but it is none the less generally a fact that cutaneous and osseous syphilis, while deforming, embarrassing and sometimes crippling, are rarely fatal, even under the most unfavorable circumstances. It should be emphasized, however, that this statement can be made only where the benign syphilis is uncomplicated by the graver lesions of the disease. The practitioner must guard himself against a tendency, where a benign lesion appears, to make diagnosis and proceed to treatment without adequate and thorough-going appraisal of the case. Thus it may occasionally happen that a cutaneous lesion will be the presenting symptom in a patient who, none the less, is a victim of serious cardiovascular syphilis. Similarly, osseous lesions may appear in patients with important visceral involvement, and what might ordinarily be a benign enough syphilis of the mucosae or of the respiratory tract will assume most serious importance because of location—as in the larynx, for example. It is important, therefore, before passing judgment upon the benign character of a syphilitic lesion, to be sure that one is not making the diagnosis merely upon the presenting symptom or upon the Wassermann, but upon a thorough-going physical examination and a careful review of the entire case.

Preparatory Treatment. In general, it may be said that a patient who presents a cutaneous, mucosal or osseous syphilis uncomplicated by cardiovascular or neurosyphilitic lesions or lesions in special sense organs, can be placed at once upon moderate doses of any of the arsphenamines heretofore described. Since, however, it is difficult under ordinary conditions of examination to detect invariably involvements of other structures which may prove to be critical in their character, it is probably the wisest plan for the average physician to institute preparation in all late syphilis at least with a bismuth salt intramuscularly. Inasmuch as there is rarely any necessity for life-saving haste in these cases, the slower action of the preparatory treatment is usually entirely satisfactory. Four to eight weekly injections of an ordinary insoluble bismuth salt usually suffice to produce marked resolution of the simpler cutaneous, mucosal and osseous lesions, whereupon the patient can then take up the standard treatment of a latent syphilitic infection as previously described, within the limits of his tolerance and the age and time factors in his case.

Nonspecific Effects.—A special caution with reference to *nonspecific effect* from treatment for syphilis should be given in connection with late lesions. An arsphenamine has a good deal of influence on the progress and healing of tuberculous, mycotic and other nonspecific granulomatous lesions, and accordingly any treatment instituted with arsphenamine for purposes of therapeutic test is always subject to this serious qualification upon the accuracy of the result obtained. It is wiser, therefore, where a question of diagnosis is raised in a skin or bone lesion, to employ mercury or even bismuth and to avoid the use of either arsphenamine or the iodides until the diagnosis is fully established or one is prepared to go ahead for therapeutic effect alone, leaving the diagnosis indeterminate.

Late Syphilis of Skin and Mucous Membranes.—A most valuable function of a visible syphilitid, particularly one of a relatively harmless character, is as an arouser of suspicion and an aid to the general diag-

nosis of the patient's condition. The value of late cutaneous lesions in this rôle is conspicuous and unfortunately too often emphasized by the physician's failure to have his suspicions aroused and to make a diagnosis, rather than the reverse. It is accordingly urged that the entire cutaneous surface of the body in every physical examination be thoroughly inspected. It is a safe general rule that no destructive lesion of the skin and no lesion which leaves a scar should ever be left unexplained in cataloging the diagnostic features of a case. The impression that the only significant late cutaneous syphilid is the solitary gummatous tumor is unfortunate, because this traditional syphilid is, relatively speaking, one of the less important cutaneous clues to a late syphilitic infection. The range and variety of late syphilids and the confusion possibilities with tuberculous, mycotic and other types of granuloma, to say nothing of malignant change, is so great that it is impossible, without an elaborate atlas and a number of differential tables, to present all differential details. None the less, there are certain general principles which, if systematically applied, will protect the practitioner from obvious errors in diagnosis. These are summarized in a table of ten basic physical characteristics with a commentary thereon.

The morphologic identification of late cutaneous syphilids depends on:

1. *Solitary character*; or at least the presence of few lesions.
2. *Asymmetry*, though this is by no means invariable.
3. *Induration*; a deep, palpable infiltration.
4. *Indolence*; a relatively low-grade inflammatory process.
5. *Arciform* configuration; the borders of the lesion polycyclic or forming segments of circles both in the individual lesion and in the configuration of a group of lesions.
6. *Sharp margination of the lesions*; in ulcers, a punched-out appearance.
7. *Tissue destruction and replacement*, with or without ulceration.
8. *Tendency to central or one-sided healing* with peripheral extension.
9. *Scar formation*; superficial, atrophic (thin and wrinkled), non-contractile. The scar retains the arciform configuration of the original lesion.
10. *Peripheral hyperpigmentation* of a rather persistent type.

Just as in the case of the primary lesion of syphilis, we can select from this group of morphologic characteristics three which carry major weight. These are, *arc*, *induration* and *scar*. The recognition of arciform and polycyclic lesions is a large part of the art of dermatologic diagnosis of late cutaneous syphilids and, in fact, often also those of the mucosal surfaces. Scalloped, kidney-shaped, cartwheeled and clumped lesions in which circles or segments of circles can be recognized in the border, when combined with induration and scar formation, especially at one side of the lesion, raise at once the suspicion of syphilitic origin. The grouped late syphilids resembling the recurrent type produce an impression on the broad surface of the skin as if droplets of water had been sprayed or thrown by hand upon a dusty surface, the successive sweeps of the arm or hand producing the arciform arrangement of the clumps. Many late syphilids are nodular and nonulcerative. The emphasis in the older teaching on punched-out ulceration and yellow, central rubbery slough applies only to the isolated gummatous lesion. Scarring is important because of its preservation of the con-

figuration of the original destructive lesion but it may ensue on the involution of lesions which have never at any time in their life history been ulcerative. Such atrophic scars may not be visible except by angular or cross illumination. They are sometimes extremely helpful in diagnosis.

The induration of the late syphilid, ulcerative and nonulcerative, is, to the experienced examiner, a very important aid in diagnosis. Only in this way is it possible to distinguish some of the psoriasiform late syphilids from common and entirely unimportant dermatoses. The practitioner should therefore never lose an opportunity to palpate undoubted syphilitic lesions in order to get the peculiar deep feel of genuine induration.

A word of caution should be given as to overstrained interpretations on these points. They are particularly apt to occur in differentiating such lesions as the stasis ulcer on the leg, where the natural tendency to produce circular or polycyclic configurations sometimes creates a false impression of the instrumentality of syphilis. If induration, arc and scar are considered together with the terrain of the ulcer, the tendency to this form of misinterpretation will be reduced to a minimum.

The blood serologic tests will, of course, continue to be the main reliance in ordinary practice in identifying cutaneous and mucosal late syphilis. In general it is true that the tests will be positive in a proportion probably exceeding 85 per cent by modern methods. The 15 per cent margin of error is, however, important, not only for those syphilitic cases which are serologically negative but for those patients who do not have syphilitic lesions but do have syphilis-positive serologic tests. This issue particularly becomes critical in the clinical differentiation of tuberculosis and malignant disease on the mucous membranes in combination with syphilis in the patient. **It should never be forgotten that the mere presence of a positive Wassermann does not prove the presenting lesion to be a relatively harmless, benign syphilid.**

In the case of sero-negative syphilitic lesions, over-reliance on certain criteria may lead to errors. These partially or wholly untrustworthy criteria include the history given by the patient, which is in error to a degree ranging from 30 to 60 per cent; pathologic tissue examination; animal inoculation; dark field examination; and finally therapeutic test, on which comment has already been made.

The histology of the late syphilitic lesion varies somewhat with its duration and character, and frequently fails to present anything distinctive. Typical gumma is, of course, granuloma and contains giant cells, plasma cells, lymphocytic infiltration, fibroblasts and even epithelioid cells in proportions that may cause very marked variations in the picture. It must therefore be emphasized that tissue examination may fail entirely to differentiate a gummatous syphilitic from a tuberculous lesion, from the mycotic gumma of sporotrichosis and even from some of the variations on the picture of small round cell sarcoma, hemangio-endothelioma and pyogenic granuloma. Only in the presence, for example, of absolutely unmistakable tubercles should the diagnosis of tuberculosis be unqualifiedly made from tissue. Animal inoculation, while slow, has undoubted value in differentiating tuberculosis from syphilis, but negative results mean nothing, and the test has no value in identifying syphilis as such under ordinary laboratory circumstances.

The inoculation of gummatous material into rabbits, because of delay and uncertainty, has no value.

Dark field examination of cutaneous late syphilids is a waste of time, for the *Spirochaeta pallida* is practically never present in sufficient numbers to be identified in this way. On the mucous membranes this point may become important because the adventitious spirochetes in the mouth and throat may occasionally be present in numbers and forms closely enough resembling the *Spirochaeta pallida* to deceive the inexperienced.

Cutaneous Syphilis vs. Cutaneous Tuberculosis.—Tuberculosis may produce upon the skin and mucous membranes, particularly about the orifices of the body, lesions which the inexperienced have great difficulty in differentiating from syphilids. The essential features, unfortunately not invariably present or present in satisfactory combinations, include, first of all, the identification at the periphery of the process, and sometimes in the apparently normal or only slightly inflammatory skin and mucosa around the central active process, of the elementary lesion of cutaneous and mucosal tuberculosis, which is the so-called apple jelly nodule or cutaneous tubercle. This is demonstrated by exsanguinating the skin at the suspected site by pressure with a thick microscopic slide or a glass tongue depressor or even with the edge of a tumbler. Through the glass, the minute miliary tubercles of a brownish translucent color may be recognized on the pale background. Translucent nodules simulating apple jelly nodules are occasionally present in the borders of syphilids, but they are usually very much coarser and softer, more often present in involved tissue and less often in normal, and therefore inclined to crust and ulcerate more promptly than the average apple jelly tubercle. Unfortunately, in some forms of ulcerative tuberculosis the rapid destruction of the tissue allows practically no peripheral terrain in which to identify individual tubercles. These cases must be diagnosed from microscopic section or other features of the case. It is important to remember that tubercle bacilli are not easy to find in lupus vulgaris and prolonged search for them may be entirely fruitless. There are also tuberculous processes on the skin such as tuberculosis colliquativa and serofuloderma, which produce only sodden, indurated areas with sinus formation in which no apple jelly nodules can be recognized. Syphilitic processes, particularly about sinuses involving bone, may produce excellent imitations of the bluish, sodden serofuloderma which surrounds the mouths of tuberculous sinuses and which, even in tuberculosis, does not contain tubercles. Examination of the pus from draining lesions is more often fruitful in some of these doubtful cases than is the examination of the tissue itself, for the pus from tuberculous lesions may contain the organism in convincing numbers and typical form.

Malignancy vs. Syphilis on Skin and Mucosae.—The differentiation of malignant change from syphilis in lesions of the skin and mucous membranes, but especially the latter, is often a critical issue. Mucosal late syphilids exhibit an alarming propensity for malignant breakdown and a lesion which may still preserve the typical morphology and even a striking response to treatment for syphilis may none the less harbor a focus of highly malignant degeneration at some point in its base or periphery. This is fortunately very much less true of cutaneous syphilids, though they do occasionally break down, especially about the face, into epitheliomas. In the effort to protect the patient with a

coincident syphilis from a failure to identify a malignant phase of the process, the following principles are of some assistance.

Tissue for pathologic examination should be taken from the harder rather than from the more elastic portion of the lesion and a number of specimens should be taken rather than one or two. It is wiser, where the lesion is fairly circumscribed, as on the lip, and the suspicion of malignancy strong, to make the excision complete and with the cautery, rather than to risk failing to identify the malignant focus by a partial biopsy or to distribute the disease through careless cutting. Accordingly, I have usually advised that patients with suspected malignant lesions occurring coincidently with syphilis be prepared for operative intervention at the time the biopsy is to be taken in order that the surgical treatment may be carried through to completion at once if any one of a number of sample sections from the tissue shows anything definite. The malignancy of mucosal lesions, whether associated with syphilis or not, is so great that too much precaution on this score cannot be taken. If the suspicion of syphilis as the sole cause of the lesion is so strong and malignancy so unlikely that it is only a shadowy possibility, a therapeutic test may be considered. Under these circumstances the test should be conducted with arsphenamine and failure to respond promptly and quite completely to two or three or at most four injections of nearsphenamine at intervals of from three to five days should be regarded as placing the diagnosis of syphilis as the sole etiology in very great doubt. In attempting to differentiate tuberculosis, malignancy and syphilis as possibilities in the same lesion, the diagnostic procedure becomes much more complicated on account of the non-specific effect of the arsphenamine, and greater reliance will usually have to be placed on pathologic diagnosis followed by nonspecific therapeutic test. On the skin, fortunately, as already stated, the problem of malignancy is much less critical than on the mucous membranes, but this does not excuse the failure to make a proper study of the border of a suspicious ulcer and at least several biopsies in the effort to identify potentially malignant foci. Cleveland White and Weidman¹¹⁹ have directed attention to possible error even here in the diagnosing of epithelioma from aberrant epidermal proliferations which are not really malignant. The presence of associated lymph node enlargement, particularly in lesions on the mucosa, cannot be invariably relied on for differential purposes unless a gland is removed for histologic examination. Gumma of the lymph nodes, to be mentioned presently, may occur; septic absorption from a broken-down gumma may cause a certain amount of glandular enlargement and associated glands in tuberculous processes are, of course, familiar. The shotty, small, malignant gland is not a sufficiently distinctive entity, it seems to the writer, to deserve excessive confidence in differentiation.

The previous commentary on therapeutic tests cannot be too strongly impressed. Even certain types of tuberculous lesions may respond to such a nonspecific drug as mercuric succinimide. The time elements are therefore important and marked delay or a retardation of therapeutic response after the first improvement must at once arouse suspicion of nonsyphilitic elements. The general rules governing the use of therapeutic tests are applicable here.

Of the mucosal late syphilids, those of the tongue seem most readily to escape suspicion and hence diagnosis. Any arciform or indurated

glossal lesion is open to suspicion and demands at least a serologic test. It is not necessary for the lesion to be ulcerative, and pain or painlessness may also be deceptive though there is a distinct tendency for the tuberculous lesion and the malignant lesion, at least in its later course, to be the more painful. On the other hand, gummatous lesions of the pharynx and tonsillar fauces may be sufficiently painful to cause marked difficulty in swallowing with resultant undernourishment and the production of a pseudomalignant or pseudotuberculous cachexia which may at first sight be deceptive. All ulcers suspected of being tuberculous should have their bases carefully examined by smears and scrapings for tubercle bacilli. It is also wise to have an x-ray of the chest, but it must not be forgotten that even apical lesions may be associated with syphilitic pneumonitis and do not therefore invariably prove the presence of tuberculosis without the support of a satisfactory pathologic specimen or demonstration of the organism. In general, the tuberculous ulcer on the mucous membranes is much more markedly inflammatory than the syphilitic ulcer; and the periphery, especially of the more superficial processes, may show the minute, glazed points that represent individual tubercles. Leukoplakia, often thought of as a late syphilitic lesion of the mucosae, is in reality the scar of an earlier lesion and must not be expected to show response to therapeutic test or the features of a syphilid in pathologic section.

The treatment of cutaneous and mucosal syphilids has perhaps been sufficiently discussed. Where they occur as solitary lesions late in the course of syphilitic infections of many years' standing and in older patients, there is no occasion for an exhibition of the heavy artillery of modern antisymphilitic treatment. A little mercury by mouth with iodide or, if the patient is in good general condition, a few injections of bismuth are all that is called for to produce a satisfactory symptomatic result. At the same time, here, as in latent syphilis, the time and age factors are important and a cutaneous syphilid in a young person is by no means to be regarded as a trifle and treated merely symptomatically. The patient should be treated for his syphilitic infection as a whole with due regard for the years of prospective duration ahead of him and the possibility that more critical lesions will be identified or the patient's defense mechanism prove insufficient if treatment is not carried through along modern lines. Cutaneous syphilids are sometimes thought of as having a certain amount of protective value or as excluding from the diagnosis such probabilities as neurosyphilis. It is unwise, in general, to rely on these impressions, which often fail to justify themselves in the individual case.

LATE SYPHILIS OF THE BONES AND JOINTS

The response of a properly diagnosed syphilitic skeletal lesion to treatment for syphilis is almost invariably highly satisfactory (90.7 per cent). On the other hand, a mistaken diagnosis may lead to prolonged semi-invalidism and incapacity and to the most shocking disfigurements, operative and otherwise. It is accordingly, therefore, proper to emphasize most vigorously that the approach to a skeletal lesion, if syphilis is to be properly reckoned with, must be medical rather than surgical at the outset. In other words, it involves the thorough-going examination of the patient rather than the hasty resort to knife or plaster.

Four Diagnostic Aids.—The morphology of osseous syphilis is much less clearly defined than is that of cutaneous syphilis; and the pictures in some 25 to 50 per cent of cases, depending on the method of approach, lack the sharp definition and specificity which one meets in more than 70 per cent of cutaneous late syphilis. Accordingly, diagnosis must often be reached through collateral aids. Of these, the routine use of *the blood serologic test stands first and foremost*. If every skeletal lesion were given the benefit of routine serologic testing for syphilis, the proportion of diagnostic errors and mismanaged cases would be very greatly reduced. The serologic tests may be expected to be positive in osseous syphilis in from 80 to 90 per cent of cases. The majority of exceptions are included under the tabetic arthropathies. The *second* angle of approach should be by way of a *familiarity with cutaneous late syphilids*. Probably because of the immunologic interrelations involved, 50 per cent of osseous syphilis, taken in the aggregate, has associated cutaneous lesions upon which a diagnosis of syphilis can be based. Bone lesions are also associated with hepatitis (11 per cent of cases) and with cardiovascular lesions, particularly in the serologically fast cases. The *third* angle of approach is by way of *the x-ray plate*. Fifty per cent of the diagnoses of osseous syphilis can be made directly from the x-ray appearances, and more than 75 per cent of the cases will show quite clearly defined though not necessarily specific lesions. A syphilitic lesion of bone or periosteum may, however, be present yet show nothing in the x-ray, particularly in early syphilis. The *fourth* angle of approach to diagnostic acumen in skeletal syphilis is *familiarity with the stigmas of prenatal syphilis*, which will be reviewed in a subsequent section.

For general diagnostic purposes the following descriptive points have considerable value. The commonest skeletal syphilids are probably those of the bones of the face and head, though a certain amount of artificial selection is probably exercised here by their comparatively easy recognition. Next after the head and face in order of frequency is syphilis of the tibia, and no examination of a patient should be regarded as complete which does not both inspect and palpate this bone. After the tibia come lesions of the shoulder girdle which are frequently so easy to recognize yet so easily misunderstood that they deserve particular emphasis for their diagnostic worth. This is particularly true of periosteal lesions of the inner third of the clavicle and the gummatous osteochondritis of the sternoclavicular junction. Syphilitic spondylitis is not rare, exceeding slightly in frequency lesions of the femur, the fibula, and the forearm and hand. Joint lesions are less commonly syphilitic than bone lesions in a proportion of perhaps one to five.

Important diagnostic aid comes from the overwhelming predominance of periostitis as a syphilitic bone lesion. In the writer's experience it appears in 53 per cent of cases as compared with 20 per cent for its next nearest competitor, osteomyelitis. This fact alone frequently makes it well worth while to extend roentgenologic examination beyond the immediately presenting lesion or chief complaint and to include in the x-ray series at least several of the long bones. This is true even though there be no palpable thickening or local tenderness. From the angle of symptomatology, pain and swelling are the two conspicuous symptoms of skeletal syphilis. Stillman's aphoristic summary, quoted by Dunlop, gives two positive and two negative signs for syphilis of the

bones—the presence of pain and swelling, and the absence of suppuration and local glandular involvement.

On two points the writer's personal observation is at variance with conventional conceptions, namely, on the importance of the nocturnal character of osseous pain and on the significance of trauma at the onset of a bone syphilid. Nocturnal pain, so frequently stressed, occurred in only 14 per cent of the series of cases here studied, and trauma appeared to be a factor in only 25 per cent.

The Syphilitic Joint.—The syphilitic joint, as distinguished from the syphilitic bone, has several important features. It is frequently stated by roentgenologists that the only distinctive syphilitic joint picture and perhaps the only distinctive roentgenologic picture in the whole field of skeletal syphilis is the Charcot joint. Certainly changes in syphilitic joints may sometimes be minimal as compared with the clinical findings and a large, fluid-containing boggy knee, for example, may show exasperatingly little to connect the process with the positive Wassermann previously or subsequently detected. In such cases a search for periosteal changes somewhat higher up on the long bones involved not infrequently gives valuable help. The almost asymptomatic bilateral hydrarthrosis of the knees in prenatal syphilis, in which the roentgenologic changes are practically *nil*, must be borne in mind by all students of syphilitic joint disturbances. True syphilitic arthritis and synovitis are comparatively rare. Osteomyelitic changes involving joints are, at least in the writer's experience, more common and it is from these that the most puzzling pseudotuberculous pictures arise. It is, of course, difficult to propose any trustworthy clinical differential criteria but it may be pointed out that the syphilitic joint thus involved shows a distinct tendency to be indolent, painless, and movable out of all proportion to the apparent extent of the involvement. Marked destruction with sinus formation, such as would be expected to produce ankylosis in almost any other osseous process, may be accompanied by a very considerable degree of usability and freedom from discomfort in the syphilitic joint. Such a criterion, of course, has only very qualified value and should be checked against the four modes of approach above described rather than accepted on its face value. In lesions of this sort associated cutaneous syphilids sometimes help greatly in diagnosis.

The Charcot Joint.—Diagnostically speaking, the Charcot joint must depend upon roentgenologic findings and its association with definite evidence of neurosyphilis for its recognition. It is interesting that this lesion occurs overwhelmingly in males in contrast to the exact opposite rule with reference to osseous syphilis in general, which is much more common in women. The blood serologic tests are distinctly unreliable in the identification of Charcot joints; for the type of tabes with which they are associated, like tabes with gastric crises, is the one most commonly associated with negative blood and negative spinal fluid. For this reason it is particularly important to search the patient for neurologic signs of tabes which can almost invariably be found to corroborate the diagnosis. In fact, it may be said that a diagnosis of Charcot joint remains uncertain until definite signs of tabes appear. Again, as in several items previously mentioned, the writer's study of osseous syphilis leads to conclusions not exactly in conformity with tradition. Pain may occur in a Charcot joint from the onset, though such is not generally considered to be the case. Many of these lesions begin with

a hydrarthrosis which may lead to confusion with the other forms of syphilitic hydrops. Hypermotility is extremely suggestive and should be looked for in every fluid-containing joint. The commonest Charcot involvements are foot, ankle, knee, hip and shoulder. Multiple joints may be affected. Trauma, at least insofar as the patient is able to identify it, is again a less important factor in the writer's experience than he had expected from general impression. None the less, patients with tabetic neurosyphilis should be routinely warned against the risk of bringing on a Charcot arthropathy by otherwise trifling injuries to their joints. A word of caution should also be given to the orthopedist and surgeon who is apt to be the first one to diagnose the Charcot joint. Although the association with a negative blood and spinal fluid is frequent in these cases, the serologic findings do not mean that the neurosyphilitic process is necessarily arrested. Accordingly, the physician in charge of the case should plan treatment appropriate to the milder grades of symptomatic neurosyphilis, even though blood and fluid provide no special indication for it. Treatment for syphilis, of course, has little or no effect upon the Charcot joint whose cause, while as yet undetermined, seems more probably trophic than anything else.

Syphilitic Spondylitis and Pseudarthrits Deformans.—The routine use of blood serologic tests for syphilis in the study of all cases of bone and joint disease will be the chief means of inspiring investigation of supposed syphilitic spondylitis and the group of arthritides of more or less undetermined nature which are definitely known to be associated in some cases with syphilis but which do not respond invariably or satisfactorily to antisyphilitic treatment. There is reason to suspect that partial or nonspecific positive Wassermanns may occasionally be obtained in these latter cases. It is a question, too, whether the response to treatment which appears in some of them and which has led to their identification as syphilitic pseudarthrits deformans, is not actually a nonspecific response with the positive serologic tests coincidental or likewise nonspecific in origin.

Syphilitic Bursitis, etc.—An interesting though relatively uncommon, or at least unrecognized, group of lesions includes syphilitic bursitis and the so-called juxta-articular nodes and fibrous gummas of the fascia, occurring particularly near the joints of the extremities. Syphilitic bursitis most frequently involves the prepatellar bursa of the knee but likewise may affect the olecranon bursae, either separately or coincidently. The gummatous infiltration of the bursa is often followed by involvement of the overlying skin, producing a cutaneous syphilid which too often fails to arouse suspicion. As a rule the lesions are symmetrical and their response to antisyphilitic treatment is prompt and complete. Juxta-articular nodes and fibrous gummas are relatively slow to respond to antisyphilitic treatment which is apt to confuse the outcome of therapeutic tests. This delayed response of all types of osseous lesions will be mentioned again under treatment.

Syphilis of the Facial and Cranial Bones.—Syphilis of the bones of the head and face, including the palate and septum, is, unfortunately, seldom recognized in its incipency. The bone necrosis which marks these cases is usually followed rather than preceded by external swelling and gummatous infiltration of the surface tissues. On the nasal septum the edema which precedes perforation has in several instances in my experience been wisely used as the indication for a blood Wassermann

test and the same rule applies to even the most trivial suggestion of sinus formation in the tissues of the hard palate. Tumors appearing upon the surface of the skull, especially when there is palpable loss of osseous tissue, even though the surface has not broken down, should always arouse suspicion. The most important element of confusion, namely, malignant metastases to the cranial vault, is fortunately relatively uncommon and most of these lesions turn out to be syphilitic when suspicion of their character is once aroused. Gummas of the jaw and the walls of the maxillary sinuses are not uncommon and are too frequently mistaken for malignant processes. Their incidence after dental trauma should always be borne in mind and the failure to heal after extraction is a useful guide to serologic testing. A very important practical consideration is the detection of syphilis in the subject of septal deviations and nasal deformities before any attempt at operative correction is made. Disastrous results may follow even trivial operations, with breakdown and destruction of the entire septum and collapse of the nasal structures into the opening. The extension of the gummatous changes to the overlying skin and subcutaneous tissue may leave a gaping hole in a surprisingly short time. Similarly, gummatous extensions from syphilitic involvement of the hard palate may produce atrocious cicatricial damage in the entire nasopharynx. These accidents occur perhaps somewhat more frequently in prenatal syphilitic infections than in acquired cases and could be largely avoided by the routine practice of performing a serologic test for syphilis before any operative procedure. The caution in regard to the wise interpretation of syphilitic gummatous change as malignant applies distinctly to osseous lesions about the nose and face. A large clinic easily provides examples of mistaken diagnoses of round cell sarcoma where the Wassermann has not been used to provide a clue, especially when the maxillary bone is involved.

The major pitfalls of differential diagnosis in late syphilitic lesions of the skeletal system include "rheumatism," tuberculosis, septic osteomyelitis, and sarcoma. Lesser but none the less significant sources of error include nonspecific periostitis, postural defects uninvestigated by x-ray (syphilis of the spine), renal calculus, hemangio-endothelioma, "ununited fracture," "housemaids' knee," and malignant metastases. Rheumatism is, of course, one of the chief symptomatic "catch-baskets." The rheumatic possibilities of error range from the confusion of syphilitic synovitis in the early stages of the disease to the mislabeling of the lightning pains of a tabes dorsalis accompanied by an early Charcot joint. Dunlop¹⁵⁰ emphasizes the fact that there may be no way of differentiating syphilitic joints from infectious arthritis and insists upon a blood Wassermann test in all cases, even though markedly febrile. Nineteen per cent of the early syphilis in the writer's experience presented symptoms of a type describable as rheumatic. Patients often initiate a mistaken trend of thought in their medical adviser by their self-diagnoses of "rheumatism" and "neuralgia" in neurosyphilis. The lack of abnormal x-ray findings in the early syphilitic joint, especially in benign hydrarthrosis, helps still further to deceive the hurried examiner or one with an inadequate index of suspicion for syphilis. Against all the possibilities of error above mentioned, the combination of a routine blood Wassermann test, adequate inspection of the skin, adequate general study for collateral evidence of syphilis, particularly neurosyphilis, adequate roentgenologic aid, and a knowledge of the clinical osseous stigmas

of prenatal syphilis, furnishes the best possible protection. Nonspecific periostitis may respond symptomatically even with a single arsphenamine injection which, of course, causes confusion in the attempt to use the provocative test. Tuberculosis is probably the chief source of error in diagnosis. It is important to realize that the two diseases may coexist in the same individual, particularly from childhood, and may make the unraveling of a particular tangle almost impossible. The nonspecific effect of the arsphenamines must again be constantly borne in mind in the attempt to use therapeutic tests in the differentiation of syphilis and tuberculosis. Absence of fever, relative painlessness, preservation of the mobility of the joint, and absence of local adenopathy all tend to suggest syphilis. Roentgenologic control should be applied in all such therapeutic tests, for improvement can be detected by the x-ray in syphilitic bone lesions often before it is clearly apparent clinically. A search for cutaneous tuberculids and dermatologic assistance in their interpretation and diagnosis may save serious errors in diagnosing syphilis where the lesion is in reality tuberculous. The erroneous diagnosis of sarcoma made on syphilitic lesions of the periosteum occurs fortunately much less frequently than in pre-Wassermann days. The ablest surgeons and pathologists may be deceived by the clinical picture of syphilitic osteoperiostitis and by the dense mass of small round cells with which an early gumma may be packed. It is, of course, not advisable to delay too long an amputation for a treatable bone sarcoma, but it may at least be pleaded that if the Wassermann is positive, a fast-acting therapeutic test for syphilis under skilled direction with the simultaneous administration of an arsphenamine and bismuth may settle the differential problem within two or three weeks. A careful search in such cases for periosteal lesions in other parts of the body is important. While x-ray is, of course, frequently the major element in the diagnosis, it is unfortunately not infallible. Some diagnostic assistance may occasionally be derived from the peculiarities of the therapeutic shock or Herxheimer reaction in bone, as will be presently described.

Treatment of Syphilis of the Skeletal System.—Uncomplicated bone and joint lesions may, like the uncomplicated cutaneous late syphilids, be treated from the outset even with the arsphenamines. Where a therapeutic test is desired, this energetic treatment is necessary; for the response of bone lesions is considerably slower than those of other tissues. The minimal time in which one can expect to see a distinctive response to even an energetic course is usually three to four weeks. The Herxheimer flare-up in bone is notably delayed so that not infrequently, both in osseous and joint lesions, the third or fourth week finds the lesion still getting worse instead of better. The notable exception to this rule, however, is the rather more prompt relief of pain, which usually disappears by the end of the first week. In the earlier syphilitic periosteal lesions without marked bone changes, pain may vanish within 24 hours. On the other hand, pain also may be susceptible to Herxheimer exacerbation, and this, as Moore has pointed out, may have diagnostic value and assist in the identification of otherwise inconspicuous lesions in other parts of the body. Lesions of the palate and cranial bones may be extremely slow in response and a septum may not completely heal short of two or three years of treatment. Failure of a syphilitic bone lesion to respond within the time limits above mentioned, however, usually means that necrosed bone is still present. In such

cases **surgical intervention** is usually called for before healing will take place. In order that the surgical interference shall not extend the lesion as it would in an untreated case, it is well to postpone removal of the sequestrum until at least a course of six or eight injections of **arsphenamine with bismuth or mercury** has been given. Even more treatment may be desirable before interference in the case of an involved palate or septum. Patients with uncomplicated osseous syphilis should never be treated merely to the point of resolution of the bone lesions. The general principles applicable to the treatment of a latent case should be used once the bone lesion itself has been satisfactorily disposed of. This applies particularly to patients with prenatal syphilitic infections in whom the subsequent revival of the process may sometimes be traced to merely symptomatic treatment of earlier lesions. About half of the patients with syphilitic late bone lesions may be expected to remain serologically positive in spite of rather intensive treatment. In such cases investigation of the nervous system, cardiovascular system, and so forth, as in any fixed positive case, is called for.

It is impossible, in discussing treatment, to overemphasize the fact that surgery undertaken in advance of the detection and treatment of osseous syphilis is almost invariably disastrous rather than beneficial. If cutaneous gummas over bone could be routinely diagnosed before the too ready scalpel is used, serious damage could be greatly reduced or done away with altogether.

The Charcot arthropathy presents a special problem in treatment, and mechanical support with a hinged brace is, as a rule, the only palliative which can be offered the patient. In some instances it may be desirable to amputate the joint of an extremity, particularly where infection takes place, depleting the patient's general resistance and maintaining him in a state of chronic invalidism.

MISCELLANEOUS BENIGN LATE SYPHILIS

Gumma of the Lymph Nodes.—Without any intention of cataloging the less important rarities among late syphilitic manifestations, certain types of lesions deserve mention because they enter into differential diagnostic problems of a number of different types. Among the first of these is gumma of the lymph nodes, which is not common, yet not rare, in the white patient but, according to Hazen,¹⁵¹ comparatively frequent in the colored race. Gummatous lymphadenopathy may appear spontaneously or in association with gummatous processes in visceral structures drained by any group of lymph nodes. It is seen as a sequel, for example, of acute tonsillitis and also associated with syphilitic hepatitis. It may help to confuse the diagnosis of aneurysm where mediaspinitis is associated with enlarged lymph nodes; it may produce a clinical appearance of malignancy in association with abdominal lesions, including those of the stomach, gallbladder, and rectum; and even the axillary lymph nodes may be involved in gumma of the breast. The chief element of confusion, of course, is with tuberculous lymphadenitis, a possibility which is enhanced by the occasional occurrence of partial positive serologic tests by certain techniques in tuberculous lymphadenitis, and likewise by the rather marked response of tuberculous lymphadenitis to arsphenamine. Avoidance of the confusion to which these considerations may lead can only be accomplished by the thorough-going consideration of the individual case from every standpoint rather than from

that of any single item like the serologic test or the pathologic tissue examination.

Late Syphilis of the Male and Female Genito-urinary System.—True syphilitic involvement of the genito-urinary structures is a comparative rarity and the tendency to ascribe to syphilis clinical abnormalities in this group merely because of the presence of a positive serologic test should be deprecated. Acute syphilitic *nephritis*, for example, is practically the only conclusively identified syphilitic lesion of the kidney, though the range of possibilities extends from paroxysmal hemoglobinuria to amyloid change. Late syphilis of the *bladder* has been reported but is exceedingly rare. Syphilis of the *prostate* is rare but well authenticated, a notable description being that of Warthin.¹⁵² Gellhorn¹⁵³ has been among the chief American students of late syphilis of the *female genitalia*. Practically speaking, the occurrence of 40 per cent of uterine hemorrhage in women with syphilis of the internal genitalia and the possibility of confusion of gummatus with carcinomatous changes in the cervix are the points of major importance. Adair¹⁵⁴ has reported a literature of 46 cases of gumma of the *female breast*, one case appearing among 1674 carcinomas. Cutaneous involvement appears, as in carcinoma, with involvement of the lymph nodes, and differential diagnosis is usually dependent upon pathologic findings plus serologic test and therapeutic response. The *testis and epididymis* in the man, in contrast to the comparative rarity of genito-urinary syphilis in the woman, are frequently involved. The findings, however, are usually clinically subthreshold or escape the attention of both patient and physician. Diffuse interstitial sclerosis and gumma are the two recognized manifestations. Marked degrees of the former give rise to the so-called "billiard ball testis," a slowly developing enlargement without marked symptoms other than a dragging or aching sensation due to increased weight. The testis becomes insensitive to pressure and there may be an accompanying hydrocele. Sarcoma and tuberculosis are favorite errors in diagnosis and especially the former is sometimes insisted upon by the surgeon in the face of a strongly positive blood Wassermann reaction. The response to arsphenamine treatment is rapid enough to justify an intensive therapeutic test in such cases. As a rule, the epididymis is involved before the testicle in tuberculosis, and only secondarily and following the involvement of the testicle in syphilis. "Fungus testis" is the ulcerative gumma of the testis which is most often confused with sarcoma and teratoma.

Syphilitic elephantiasis, while a relatively uncommon lesion, is one infrequently diagnosed unless a routine serologic test is used. Most frequently it occurs about the genitalia, particularly in the woman, and, in my experience, in the colored race. There is a certain amount of response to therapeutic test which may be utilized in confirming suspicions aroused by a preceding positive Wassermann.

Syphilis of the larynx, lungs, mediastinum, and thyroid is rarely diagnosed on clinical objective findings alone, though there has been a notable increase in reported cases since the frequency of pneumonic nonresolution in syphilitic patients with coincident pneumonia has been emphasized in the literature, and more attention has thus been directed toward syphilis of the chest apart from the vascular structures.^{155, 156} Most of these conditions are recognized as by products, so to speak, of a suspicion of malignancy, or, in the case of gummatus mediastinitis, of

lymphoma, substernal goiter, or aneurysm. Tuberculosis of the larynx and trachea is important to the syphilotherapist because it is one of the best illustrations of the potential gravity of a comparatively trivial lesion on account of its location. Therapeutic shock and edema involving a gummatous larynx may produce fatal obstruction and accordingly must be approached with all the circumspection in treatment that is applied to the most critical lesions of the brain, myocardium or viscera. In the differentiation of mediastinal processes, arsphenamine should not be used at the outset, not only because of its nonspecific effect, but because of the possibility that a mediastinal shadow may abruptly turn out to have been an aneurysm which becomes unfortunately demonstrable at autopsy in the rupture following therapeutic shock.¹⁵⁷ The approach to such lesions in therapeutic test should therefore be by way of mercury, iodide, or perhaps very moderate doses of bismuth. Gummatous thyroiditis is not differentiable from malignancy on purely clinical grounds, and tissue examination is always necessary.

Gumma of the pancreas and suprarenals, as well as interstitial pancreatitis, and diffuse involvement of cortex and medulla, in the case of the suprarenals, present no symptoms distinctive of syphilis.

RECURRENT AND LATE SYPHILIS OF THE EYE AND EAR

This section is not intended either as a description of eye lesions or a guide to diagnosis. For this information the reader is referred to ophthalmologic texts and consultation. It is merely intended here to point out certain useful principles which the physician may apply when called upon to work with eye lesions in syphilis or to apply in protecting his patient from important eye complications. All intelligent work with syphilis of the eye requires the constant and intimate coöperation of an ophthalmologist for the best results. Physicians in other fields of work usually find it safest to regard themselves as ophthalmoscopic amateurs in attempting to diagnose or follow the course under treatment of syphilitic eye lesions. Two types of eye lesions are of particular gravity because of the rapidity with which they may produce serious and lasting damage and because of their frequent association with lapses in treatment or insufficient treatment for which physician or patient may be responsible. These are *optic neuritis* in the two forms of choked disk and infectious optic neuritis; and *retinitis* with or without involvement of the choroid. Most frequently in the relapse forms the two may be combined and the inflammatory changes involving the nerves likewise involve the retina. Choked disk is a rather frequent associate of basilar forms of neurosyphilis. It would doubtless be more frequently detected by a practice of routine examination, but is usually only recognized when the meningeal headache and impairment of vision are first noted by the patient. The loss of vision under inflammatory changes is extremely rapid and calls for immediate and intensive measures. Where the process is associated with basilar cerebral lesions it is usually advisable to give at least a few injections of **mercuric succinimide** daily together with **sodium iodide intravenously, or in large doses by mouth** [100 Gr. (6.66 Gm.) three times daily at least], following which an arsphenamine in moderate and then in full dosage is urgently indicated. Vigorous emphasis should be placed upon the entire safety of the arsphenamines in these acute conditions of the optic nerve and retina, for the tradition, initiated by Ehrlich, that arsenical drugs en-

danger the optic nerve has been taken up by ophthalmologists with greater seriousness than subsequent experience has justified. The tendency, therefore, may be to undertreat these lesions rather than to overtreat them and to leave the patient with a serious grade of secondary optic atrophy and retinal degeneration. The drug is especially well tolerated where the process is purely local and inflammatory, and the longer preparations are only appropriate to those cases in which choked disk is the expression of a rise of intracranial pressure from brain gumma or high-grade syphilitic meningitis.

The various forms of *choroiditis* and *choriorretinitis* which may produce rapid and destructive vascular lesions of the choroid and retina with hemorrhage, exudation and opacities likewise respond very rapidly and satisfactorily to thorough-going **arsphenamine** treatment. The therapeutic shock effects in these lesions seem slight or absent and no time need be lost in prolonged preparation.

It is important to point out that the arsphenamines have marked *nonspecific effect* upon choroiditis and uveitis associated with focal infections and tuberculous processes, and that for this reason, where the diagnosis is in doubt, it is better to employ bismuth or mercury. Even mercuric succinimide seems to have a certain amount of beneficial nonspecific effect on nonsyphilitic lesions of the uveal tract.

Syphilitic lesions of the anterior portion of the eye do not in general require preparatory treatment before the use of an arsphenamine. One is repeatedly impressed by the extreme importance of thorough-going atropinization and the inability of the physician who sees the patient only occasionally, and of the patient who is solely under the care of members of his family in the intervals between visits, to carry out a proper instillation of atropine to secure an adequate dilatation. The matter should be constantly kept under observation, and if a member of the family must instill the drops, he should be most thoroughly trained by the ophthalmologist himself. The sequel of failure to use atropine promptly and effectively is, of course synechial adhesions and the possibility of secondary glaucomatous change. Syphilitic iritis is a particularly insidious form of relapse and is subject to recurrence in predisposed cases under anything but the most thorough and persistent treatment. Here, as in the before-mentioned eye complications, ophthalmologic tradition may lean too much toward the older and less effective measures, and determined and persistent use of the arsphenamines is therefore vigorously urged.

The appearance of an eye lesion in the clinical course of syphilis demands a thorough rehearsal of the case for the detection of stigmas of prenatal syphilitic infection. So important are eye lesions in the life history of prenatal syphilis that in a survey of cases in the writer's experience only 22 per cent of the patients¹² were found to have normal eyes. Interstitial keratitis, which constitutes 52 per cent of the eye lesions of prenatal syphilis and approximately 0.5 per cent of all eye disturbances, is one of the serious special problems of the disease. It leaves a residue of actual damage to vision estimated by Igersheimer¹³ as 40 per cent of all patients affected, only 60 per cent recovering useful vision. It may be said, fortunately, that these statistics are based rather upon older than newer methods of treatment, but none the less they indicate the crippling capabilities of the complication. The onset of interstitial keratitis is commonly between the ages of 5 and 16,

though it may appear for the first time as late as 30 years of age. It is more common in girls than in boys. Lowering of general resistance, intercurrent infections, and so forth, act as predisposing causes but despite this, interstitial keratitis has a peculiar flair for independent action and may attack the patient suddenly without the slightest evidence of predisposing influence, other than the underlying syphilitic infection. The earliest symptom is slight ciliary congestion followed by the appearance of small, grayish, infiltrative deposits either toward the periphery or in the center of the cornea. Circumcorneal injection of the sclera, suggesting an episcleritis, may be the first sign that attracts the patient's attention, or there may be a slight smarting, lacerimation and discomfort in the light, the forerunner of the intractable photophobia from which these patients suffer. With the extension of the process, marked degrees of vascularization and opacity occur from which complete recovery, even under the most intensive treatment, is too much to expect. The physician who will accustom himself to examining the cornea with a lens for cloudy spots and faint grayish stippling whenever a child complains of sore or running eyes or has a "conjunctivitis" or "pink eye," will contribute inestimably to the diagnosis and perhaps the ultimately successful treatment of interstitial keratitis. Even the protracted "cold" which cannot stand strong light is a proper object for the quick survey of stigmas and the taking of a blood Wassermann test. Some degree of iritis usually accompanies an interstitial keratitis and is responsible for increased pain and lacerimation. The importance of thorough-going atropinization is reiterated. While the disease tends to run a self-limited course, relapse is very common, occurring in from 18 to 22 per cent of cases. Under the older treatment régime it was a rare thing for the second eye to escape involvement. Today, under intensive modern treatment with the arsphenamines and bismuth as indicated by the studies of Carvill and Derby,¹⁶⁰ there seems hope that the process, if treated early in the one eye, may be prevented from appearing in the other. The contrast between the outcome in adequately treated and in inadequately treated cases is so extreme, and, in fact, often so shocking that there can be no reasonable question of the desirability of early detection and early intensive therapy. The possibility of confusion with tuberculous interstitial keratitis must not be forgotten in the haste to confirm a diagnosis of prenatal syphilis in a doubtful case. Treatment is discussed in the section on Prenatal Syphilis.

Primary optic atrophy is the last of the eye lesions requiring special comment, and this particularly from the standpoint of treatment. It appears usually as part of the syndrome of *tabes dorsalis*, whether in the acquired or prenatal infection. The familiar grayish or gray-white disk is as nearly a typical affair as any amateur examining the fundus can expect to identify. No eye lesion produced by syphilis has a more completely unfavorable prognosis or runs a more unaccountable course, with or without treatment. Primary optic atrophy is the one eye condition in which the writer would urge the extreme of caution with reference to the precipitate use of an arsphenamine. Whether through the direct arsenical effects of the drug, or through therapeutic shock acting upon some center not as yet identified, there seems to be not only no advantage but positive danger to eyesight in the precipitate use of this drug by ordinary intravenous technic. Moore,¹⁶¹ whose experience is the largest of any American author, however, in a study of

the effects of intraspinal therapy in primary optic atrophy, believes that this effort to localize the treatment to the nervous system has distinctly beneficial results. The number of cases in which intracranial treatment has been tried is still too small for evaluation, but it must be confessed that the method seems to offer very little. In fact, the whole treatment of primary optic atrophy contains an element of the unaccountable which may lead one drug or system to achieve strikingly good results in one case, where precisely the opposite technic works equally well in the next. Unfortunately, no method is capable of producing regenerative changes in such a condition, and the most that can be hoped for is something approaching arrest short of complete blindness. The systematic use of bismuth, while at least not accomplishing anything noteworthy, seems to be as free from the likelihood of doing harm as any of the constitutionally less effective older methods. Neurologists have noted the tendency of the neurosyphilitic involvement of other structures to come to arrest as a primary optic atrophy develops, but this is small consolation for the loss of sight.

No mention is here made of the extra-ocular palsies and third nerve lesions of neurosyphilis, as they are, in general, extrinsic to the eye.

The Ear.—Syphilitic lesions affecting the hearing in syphilis are usually traceable to involvement of the eighth nerve, either by a meningeal or a deeper central process. Late syphilis of the middle ear, while described, must be a rarity. Quite a large proportion of the lesions is traceable to prenatal rather than acquired syphilis. Deafness, either dating from birth or coming on during childhood, occurs in 10 per cent of prenatal syphilitic patients. As a rule it is total and, if it develops before the tenth year, is very apt to lead to deaf-mutism. The partial or fluctuating types are open to question as to whether they are syphilitic at all, although they occasionally improve quite markedly under treatment for the disease. Typical syphilitic eighth nerve deafness is generally complete within a comparatively short time and is irremediable. In some instances promptness and extreme persistence in treatment may lead to improvement, but the writer's impression has been that these changes are quite often traceable rather to the acquisition of lip-reading habits than to actual symptomatic change. Deafness occurs in from 1 to 4 per cent of tabetics. A rather important but not common group of lesions centers around the syphilitic involvement of the labyrinth. These manifestations take the form of Ménière's syndrome subject to confusion with petit mal, with hysteria, and with the influence of other infections and migraine upon the labyrinth. Vertigo appears as a symptom in from 4 to 13 per cent of tabetics, but the complication probably is not exclusively traceable to the labyrinthine change. In the writer's experience the response to a soluble mercurial, to bismuth, and to large doses of iodide, including its intravenous use, is often more satisfactory than to the arsenicals. Syphilitic eighth nerve disease, if accompanied by lesions of other nerves, particularly of the third, is expressive of general involvement of the nervous system and calls at least for a spinal fluid examination.

SPECIAL DIAGNOSIS AND TREATMENT OF LATE VISCERAL SYPHILIS

Syphilis of the Gastro-intestinal Tract.—From the general standpoint, attention should be directed in dealing with gastro-intestinal symptoms in syphilis, first, to the actual rarity of syphilitic lesions of

the gastro-intestinal tract in patients who complain of gastro-intestinal symptoms in association with their syphilis. Less than 5 per cent of gastro-intestinal symptoms in syphilis are found to correspond to an actual gastro-intestinal lesion. In the second place, neurosyphilis is responsible for at least half of the symptoms which would otherwise pass as functional or neurotic in patients with gastric symptoms and coincident syphilis. The abdomen is literally the playground of neurosyphilis from the symptomatic standpoint and this fact leads to a disconcertingly large proportion of errors in diagnosis due to inadequate examination and to operative intervention which could have been avoided had the clinical and serologic evidence for syphilis been recognized. Hypochlorhydria is probably the commonest functional lesion associated with syphilis of the gastro-intestinal tract, being present in 50 per cent, with 38 per cent approximately normal. Roentgenologic examination yields a conspicuously small harvest, 84 per cent of the patients studied by Brown and the writer⁴⁴ having absolutely negative x-ray findings. The negative serologic blood test and the negative spinal fluid do not by any means eliminate syphilis from the explanation of a gastric syndrome. This combination, as in the case of Charcot joint, occurs in the type of tabes in which gastric crises are most frequent and in which the diagnosis must be made practically entirely by neurologic signs plus the periodicity of recurrence of the gastric disturbance without other explaining factors. How little this is understood, particularly by surgeons, is evidenced by the fact that one-third of the needless laparotomies performed on our patients were done for gastric crises masquerading under other diagnoses. It is essential, therefore, that the syphilitic patient in whom gastro-intestinal symptoms are conspicuous be studied, not so much with the expectation of unearthing a gastric lesion as such, as with a view to detecting the possible underlying neurosyphilitic complications instrumental in at least half of the cases. The larger part of those in whom a neurosyphilis cannot actually be demonstrated respond in a gratifying way to antisymphilitic treatment and give what may be regarded as positive therapeutic tests in 70 per cent of cases.

Of the actual syphilitic lesions of the stomach, much interest attaches to syphilitic gastric ulcer,¹⁶² which can be convincingly demonstrated by therapeutic test and which deserves fuller study from the clinical standpoint than it has received. Warthin¹⁶³ has demonstrated the *Spirochaeta pallida* in gastric ulcers and in ulcerative lesions of the jejunum in syphilitic patients. True gastric late syphilis is very probably homologous in morphology and development with nodulo-ulcerative and infiltrative late syphilis of the cutaneous surfaces of the body. There is a distinct tendency to multiple ulceration, the infiltration has the characteristics of gumma, and the deformities induced by cicatrization, including hourglass stomach and the diffuse fibrosis of leather bottle stomach, are quite what might be expected from what is known of the syphilitic lesions of other parts of the body. The details of the clinical differentiation of gastric syphilis from gastric carcinoma and other organic gastric lesions should be sought in the special texts, in the writings of Eusterman,¹⁶⁴ of Carman,¹⁶⁵ and in O'Leary's¹⁶⁶ recent summary. Fortunately, the blood Wassermann reaction is practically invariably positive in these cases and the most critical issue confronted by the therapist is that of treatment differentiation from malignancy.

In a negative way it should be said that achlorhydria and retention do not disprove gastric syphilis and that extreme degrees of loss of weight may occur in gastric syphilis as in carcinoma. A palpable mass, hemorrhage, and rapidly developing anemia speak strongly for carcinoma. The general rule applicable to the question of operative exploration versus therapeutic test in any given case can be stated in these terms: Exploration is indicated in spite of the presence of a positive blood Wassermann if the lesion is early and operable and the patient is in good condition. On the other hand, if the lesion seems advanced or is in an inoperable situation, treatment for syphilis must, of course, be resorted to at once. The reason for giving operative exploration this degree of prominence lies in the possibility of nonspecific response in carcinomatous gastric lesions. Even while exploration is given precedence, it is well to recall that gastric syphilitids respond remarkably to treatment and that when the malignant possibility is eliminated it is wise for the surgeon to reduce operative resections to a minimum unless needed to relieve actual obstruction. Really amazing functional recoveries take place in syphilis of the stomach under appropriate systemic treatment.

The treatment of true gastric syphilis requires no preparation unless complications in the heart, nervous system, or liver can be identified. The response to **arsphenamine** is one of the most gratifying in the whole field of modern treatment.

Duodenal ulcer, while not thus far definitively proved to be syphilitic, has an interesting and very definite association with *tabes dorsalis*, to which attention has recently been called by Hunt and Lisa.¹⁶⁷ Duodenal ulcer recognized in the examination of patients with neurosyphilis often shows a striking response in relief of symptoms when treatment for the syphilitic infection is begun, though the ulcer, to judge by roentgenologic signs, does not necessarily disappear.

Syphilis of the intestine and upper colon is of such excessive rarity that any suspected case must be made the subject of elaborate special study from which the diagnosis is usually likely to emerge by elimination and with considerable qualification on its accuracy. *Leukoplakia of the rectum* is capable of directing attention to the possibility of systemic syphilis. *Stricture of the rectum* due to syphilis is perhaps less common than is generally considered to be the case. The effects of previous operative trauma, dilatation, and so forth, must be taken into account in estimating the importance of a syphilitic factor in any given case of stricture associated with a positive serologic test.¹⁶⁸ The treatment of these cases uncomplicated calls for no special precaution with reference to preparation. It is particularly desirable to **exclude protozoal infections of the upper and lower intestinal tract in these cases before arsphenamine treatment is begun** because of the nonspecific effect of the arsphenamine upon the protozoal infection. Treatment for syphilis, while occasionally somewhat beneficial in chronic ulcerative colitis, rarely has a sufficiently marked good effect to produce confusion.

Syphilis of the Liver and Spleen.—Here again, as in the case of true syphilis of the gastro-intestinal tract as distinguished from gastro-intestinal symptoms in syphilis, it is wise to remember that hepatic and splenic syphilis are comparatively rare, while syphilitic pseudosymptomatology apparently involving these organs is one of the real pitfalls of abdominal diagnosis. While syphilis of the liver may be associated

with complete and undoubted serologic negativity in the blood, this occurrence is in all probability rare and the diagnostician is usually forewarned of the possibility of the disease by the practice of taking a routine blood test on all patients raising questions of abdominal diagnosis. Syphilis of the liver should not be thought of merely in terms of isolated or multiple gummas. Its clinical manifestations fall under at least six heads which provide an extraordinary variety of symptoms and signs and extraordinary possibilities for mimicry of other pathologic processes. The clinical types include, (1) early acute benign hepatitis; (2) syphilitic destructive hepatitis or acute yellow atrophy; (3) mild chronic hepatitis of latency; (4) diffuse and localized gummatous hepatitis; (5) chronic interstitial pericellular cirrhosis of heredosyphilis; (6) perihepatitis.

The first of these is the commonest cause of mild jaundice with slight hepatic enlargement in the course of early syphilis or as a feature of relapse in the later months of the first year. The second is the fulminating, critical, and highly fatal complication, fortunately extremely rare. The onset is insidious, with mild but steadily deepening jaundice, malaise, anorexia and vomiting, with or without fever. Muscular aching and severe abdominal cramps followed by a toxic condition, emaciation and a typhoid state supervene. The liver, at first markedly enlarged, shrinks rapidly; ascites may appear early; hemorrhages from the bowel, and purpura are not uncommon; and as the intoxication becomes severe, delirium, headache and maniacal symptoms develop. The late symptoms are sometimes suggestive of meningitis or uremia and severe nephritis may be a complication. Leucine and tyrosine crystals in the urine are helpful in diagnosis but not invariably found. A rapid rise in blood urea may occur. In contradistinction to the treatment of other forms of syphilis of the liver, that for syphilitic acute yellow atrophy must be intensive, and in all probability would best be conducted with bismuth and iodide, thus avoiding the hepatotoxic effects of arsenic.

"Latent" syphilis of the liver, as recognized by 10 per cent palpable livers in the routine examination of patients with latent and late syphilis, may be treated energetically in accordance with the ordinary standards for a latent syphilis. Care must be taken, however, to be sure that no signs suggestive of cirrhotic change and ascites have appeared.

Late diffuse and localized gummatous hepatitis, the former giving rise to the cirrhotic picture and the latter to the various types of multiple gummatous tumor formation in the liver tissue with all types of intermediate and mixed lesions, constitute, together with the perihepatitis which is almost invariably associated, the large body of cases of late syphilis of the liver. All three types of lesions may develop and progress simultaneously, the clinical behavior varying with the proportion that interstitial fibrosis bears to localized gummatous formation, and with the location and extent of the perihepatitis. A large gumma projecting into the portal fissure may produce ascites by pressure on the portal vein quite as effectively as a diffuse interstitial fibrosis. Jaundice may arise from blocking of the minor bile ducts by a diffuse process or from the pull of a band of fibrous tissue; or from distortion produced by scar tissue in the region of the hepatic duct. These combinations and permutations give to the clinical picture of late hepatic syphilis an extraordinary imitative capacity. The distortions produced by structural change combine with the subjective symptoms of pain and the occurrence of fever,

abdominal spasm, and so forth, associated with the localized peritonitis which is a feature of perihepatitis. The result, therefore, may be clinically perfect imitation of gallbladder disease, pancreatic disease, renal disease, or malignant degeneration and metastasis. These mimeries readily account for the extraordinary difficulty of diagnosis in syphilitic hepatic disease and the relatively small proportion of patients whose real condition is correctly named and described ante mortem or before operative exploration. Summarized from the writer's own experience in the study of 73 cases,¹⁶⁹ the chief sources of diagnostic error in order of frequency include, (1) failure properly to use the Wassermann; (2) deceptive physical findings; (3) supposed gallbladder symptoms; (4) supposed renal symptoms or signs; (5) malignancy suspected; (6) gastric ulcer diagnosed and not found; (7) gastro-intestinal x-ray omitted or misread. The miscellaneous sources of error approximate in frequency those of gallbladder symptoms. The failure to use the Wassermann in all abdominal diagnosis has already been sufficiently commented upon in connection with other types of syphilitic lesions. Sixty per cent of the observed errors in diagnosis arose from the attempt to interpret physical and particularly palpatory findings in the abdomen. Tumors of the left lobe of the liver are notoriously capable of presenting the most deceptive findings in this particular. Demonstration of the connection of a mass with the liver, and the combination of tumor of the liver and enlarged spleen, both offer important diagnostic clues.

The importance of syphilitic pseudogallbladder symptoms deserves vigorous emphasis. There is not a single phase of gallbladder disease which syphilis cannot reproduce in letter-perfect form. In particular the presence of fever and chills does not eliminate syphilis; the attacks of pain in syphilitic gummatous hepatitis may be indistinguishable from those of gallbladder disease; continuous pain in the region of the gallbladder may be present; there may be distinct attacks of jaundice, with pain, and even leukocytosis may be noted. In 20 per cent of the cases observed by the writer the resemblance of symptoms in syphilitic hepatitis to those of lesions of the kidney was the source of error. The problem of *differentiating malignant from syphilitic involvement* of the liver in the presence of a positive blood test for syphilis may be insurmountably difficult without exploration. The routine examination of the gastro-intestinal tract by x-ray and test meal needs no emphasis. The question of malignancy cannot be eliminated merely by short therapeutic test. Where this question has once been raised, observation over a period of two years or more may be necessary before one can be fully satisfied of the correctness and exclusive character of the diagnosis of syphilis of the liver. The appearance of definite new masses under treatment, especially elsewhere in the abdomen, strongly supports malignancy. *Hemorrhage* into the gastro-intestinal tract is sometimes the first clue to a syphilis of the liver and spleen in which a cirrhotic type of involvement has progressed insidiously without marked palpable enlargement. *Duodenal ulcer* may be suggested by the perihepatic symptoms and they may even, in occasional cases, owing to radiation upward into the chest, simulate *anginal attacks* though usually the anginal seizure is much the briefer of the two. Protection from error associated with *gastric crises* can be had only through thorough-going examination of the patient with special attention to the findings in the nervous system.

Jaundice is so important a symptom of syphilitic liver disease that

a summary of the differential procedure as it can be carried out by the average physician seems justified. When a jaundiced patient with syphilis presents himself, if arsphenamine has been given within a week or two and there are signs of itching skin and beginning dermatitis, **sodium thiosulphate** should be employed **intravenously** in doses of from 0.5 to 1 Gm. (7.5–15 Gr.) every other day for several doses and the effect watched. **Glucose** may likewise be given **intravenously**, 10 to 20 cc. of a 50 per cent solution. The condition is perhaps an arsphenamine toxic jaundice and the patient may develop an exfoliative reaction. If the patient has not been treated for syphilis, the condition is more likely to be syphilitic and a decision must be made as to whether the process is early or late. If it is early (patient with a secondary eruption or its residue), treatment with neoarsphenamine may be begun after a week of bismuth or mercurial preparation (soluble salt). On the other hand, if the infection is not recent, all the factors that enter into the diagnosis of hepatic injury must be considered and painstakingly eliminated. If the decision is in favor of syphilis as the cause, treatment should be begun as will presently be described for late hepatitis. If the patient has had treatment for syphilis in the past few weeks, months, or years, it should not be too readily concluded that he is suffering from a toxic arsphenamine jaundice. He may be placed on the régime for epidemic infectious jaundice. His symptoms in the right hypochondrium should be interpreted with reserve and operation should be resorted to only after persistent jaundice has failed to respond to the catarrhal regimen or to later treatment for syphilis. Fulminating jaundice with toxic symptoms should be carefully searched for evidence of recent syphilitic infection, since if it can be found the outlook by intensive treatment is quite good though absolutely *nil* without it. The possibility of an early toxic pregnancy must be kept in mind in women.

Treatment of Late Syphilis of the Liver.—The induction of therapeutic paradox is the ever-present and almost unavoidable danger in the treatment of syphilis of the liver by modern methods. This is, if anything, even a better field for its demonstration than that of cardiovascular syphilis. So sound is this generalization that the writer's own views with regard to the use of arsphenamine in syphilis of the liver have year by year undergone gradual modification tending toward an almost complete exclusion of the drug. The advent of bismuth and of bismuth arsphenamine sulphonate has only emphasized this change in viewpoint, for arsphenamine and neoarsphenamine as such have become virtually unnecessary in dealing with this particular syphilitic lesion. If it were possible to differentiate sharply a large localized gumma of the liver from gumma associated with diffuse involvement and cirrhotic change, it is conceivable that arsphenamine might retain a place in treatment. It is certainly true that highly satisfactory results are occasionally produced by what, on reflection in the light of later experience, would be classified as foolhardy use of an arsenical. **Consistent adherence to the more conservative and slow-going methods of treating hepatic syphilis, however, is the wisest course for practically every case.** If there is any sign of fluid or the case is of longstanding and of insidious onset, **hospitalization** is highly desirable, and a period of from four months to a year of **mercury and iodide** usually constitutes the safest beginning. It is surprising how much can be accomplished in these cases by the use of 2 Gr. (0.13 Gm.) of mercury with chalk

three times a day and potassium iodide, 20 to 30 Gr. (1.33–2 Gm.) three times a day by mouth. After a month of such treatment, **inunctions** may be substituted, with a course of not less than 40, and after another three months small doses of bismuth intramuscularly may be considered. At times it seems as if the iodide by mouth either as an inorganic or an organic salt is all that is required to start the favorable progress toward restoration. If an **arsphenamine** is to be used because of diminished renal tolerance in the later months of treatment, or because of intercurrent anemia or the debilitating effect of prolonged mercurialization, **bismuth arsphenamine sulphonate** may be employed in doses ranging from 0.025 Gm. to 0.1 Gm. every third to seventh day on a very gradually ascending dosage scale. Prolonged rather than intensive treatment, with alternations of medicaments rather than absolute rest intervals, seems in the aggregate to yield the best results. The control of ascites in the more difficult cases should not be accomplished by tapping if this is in any way avoidable. **Restriction of fluids by mouth, brisk purgation**, the use of **novasurol**¹⁷⁰ as a diuretic and most recently the diuretic effect of **sodium bismuth tartrate**, as investigated by Hanzlik,⁹⁸ should be utilized. The **Talma-Morison operation** of suturing the omentum to the abdominal wall is sometimes very helpful¹⁷¹ and may well be performed where operative exploration for diagnosis reveals a syphilitic cirrhotic process. Therapeutic tests for hepatic syphilis become, as will be seen from the foregoing schedule, rather long-drawn-out affairs. Not less than three or four months may well be required for a favorable reaction; and one to three years will be necessary for anything approaching recovery. In the therapeutic test for cancer, the patient usually rapidly declines under treatment. The writer's own experience with the treatment of 53 patients with hepatic syphilis indicates that methods even somewhat more intensive than those above described, but in all cases involving at least four months of mercury and iodide preparation before the exhibition of an arsphenamine even in the smallest dose, are capable of yielding 58 per cent of excellent improvement, with slight to fair improvement in 18 per cent of cases.¹⁷² Persistence, knowledge of when to go ahead and when to allow rest intervals for recuperation, and lifelong observation and therapeutic control are all important factors in an ultimate good result.

Splenectomy.—This therapeutic procedure invoked in the treatment of persistent anemia in late syphilis accompanied by splenic or hepatosplenic disease and also used therapeutically in dealing with the enlarged spleen of syphilis has occasional, though undoubted, advantages, but is technically difficult and has a by no means negligible mortality. It should not be invoked until a year of effective antisymphilitic treatment has failed to demonstrate ability to control the situation by other methods.

SPECIAL DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR SYPHILIS

Cardiovascular syphilis even more than neurosyphilis is the critical diagnostic and therapeutic problem of the late aspects of the disease today. Bruusgaard's¹⁷³ clear-cut demonstration that cardiovascular disease is the Nemesis of syphilitic infection and the outcome of more than a third of fatal syphilis cannot be too constantly borne in mind or too frequently impressed upon the medical student and upon the practitioner. Even the earliest clinical recognition of vascular involvement

in the disease is unhappily comparatively late. Generations of bowing at the shrine of the spectacular in physical diagnosis has tended to make it still later. The cor bovinum and the hat-box aneurysm, the thrill, the buzzing and whirring, the heave, the sound of the pistol shot, have blunted the sense of the practitioner for the still, small signs and symptoms of the preventable onset of syphilitic cardiovascular disease. Until teacher and textbook turn from the parading of consequences before the student of medicine to urge him to devote his energies to anticipatory watching, to habitual suspiciousness and observation, and to the acute analysis and ferreting out of veiled beginnings, syphilis of the heart and aorta will remain the great burying ground of the disease and the clinician's perpetual Waterloo at the hands of the postmortem pathologist.

The routine application of serologic tests, among which is specifically included a precipitation as well as a complement fixation procedure, in every medical examination would immeasurably further the cause of prevention in syphilitic heart disease by the detection of syphilis in spurious latency. But in vascular syphilis, there is reason to believe that as much as a fifth of cardiovascular syphilis may escape the clinician whose suspicions are only aroused by a positive serologic result. The earlier the case, one would think, the more effective the blood test. It cannot be too vigorously impressed upon the physician in charge of a patient with syphilis that complete serologic negativity within the first five to ten years, coincident with indubitable lesions, is entirely possible. The writer has himself watched patients develop cardiovascular syphilitic lesions even under fairly thorough modern treatment for syphilis and with practically continuously negative serologic tests. This emphasis on the untrustworthiness of the negative, however, should be coupled with an emphasis on the very great importance of even slight degrees of positiveness in the serologic control of a patient between the second and the fifth year of his infection. Coupled with this tendency to relapsing or partial positives and also the presence of a fixed or irreversible positive, emphasis should be placed on the suspicion-arousing value of a gradual sharpening and accentuation, a roughening of the aortic second sound, together with a gradual rise in blood pressure, particularly diastolic. It is realized, of course, that these symptoms may be accompaniments of essential hypertension in the young adult, but if the young adult has syphilis the therapeutic indications become so definite that it seems unwise to becloud the issue at the moment by too much emphasis on other possibilities. With these physical signs appears the first suggestion of slight enlargement of the heart with broadening of the base and outward displacement of the apex impulse.

Accompanying, but in some cases following, the earliest appearance of suspicion-arousing signs one must reckon paroxysmal dyspnea, especially nocturnal; the sense of precordial distress, or later pain; palpitation and dyspepsia. These form a tetrad which, though not distinctive of the syphilitic heart, must at once direct attention to the heart in the patient with syphilis. Pain, dyspnea, hoarseness, sometimes transitory, and cough rank first in the symptomatology of aneurysm. The carefully taken history is therefore invaluable in the interpretation of the cardiovascular situation when the patient presents himself to the examiner or consultant for the first time, and it should by no means be disregarded by the physician who has had the patient under observation for a period

of years. The physical signs previously mentioned, certainly not distinctive though suspicion-arousing, pass over in the fourth to the eighth year, or later, into the ringing or tambour aortic second sound and then into the early systolic murmur at the aortic area. This murmur is transmitted along the sternum and often heard best for a time at the xiphoid process. At this time the enlargement becomes more definite, the hypertension more clear-cut. In the syphilitic patient, the duration of whose infection is a matter of question, no history of the disease is obtained in 33 per cent of cases, in the writer's experience. The provocative procedure at this time may be dangerous and if coronary involvement underlies any of the symptoms, may even be fatal. The repetition of serologic tests for a number of times adds 10 to 15 per cent to the possibility of obtaining a positive. At this stage in an occult cardiovascular syphilis, 54 per cent of the writer's patients showed evidence of concomitant neurosyphilis, and 40 per cent had abnormal spinal fluids, an important clue, therefore, in identifying the presence of a concealed syphilis, but unfortunately difficult to popularize because the early cardiovascular case presents so little to make an intensive investigation seem necessary to either patient or physician. Too ready an invocation of "rheumatism" as an explanation of Wassermann-negative aortic lesions seems to the writer a criticizable feature of present-day practice. Syphilis itself, for one thing, has too much "rheumatic" symptomatology to make the history wholly trustworthy. Acute rheumatic fever in the history is, of course, a different matter, though a possible coincidence. The impossibility of making accurate diagnoses of incipient syphilitic cardiovascular disease justifies a wider and more intelligent use of the therapeutic test in young persons presenting, together with presumptive evidence of syphilis, the earliest suggestive indications of aortic disease. At this period in the life history of a syphilitic heart or aorta, the comparatively greater myocardial reserve, the presumed better condition of the coronary vessels and the better general tolerance of treatment by the patient, provide a priceless opportunity for arresting an unknown proportion of syphilitic cardiovascular disease in its beginning. It is the duty of the syphilologist, therefore, to urge upon those who see and study hearts as such, a greater willingness to perform therapeutic tests for syphilis in early aortic lesions, even though the blood serologic tests may be negative.

In the early diagnosis and consequently the effective attack on cardiovascular syphilis, the x-ray and the electrocardiograph deserve critical consideration. Many English and American observers have apparently been disappointed by the roentgenologic evidence for or against aortic disease and the decision of an alert clinician after thorough study of the patient's signs is, the writer believes, the more important element in diagnosis. When aneurysmal dilatation is well established or the aorta markedly widened, the x-ray, of course, becomes more essential, but the indication for it is often predicted by the adequate physical examination of the chest.

In the fully developed aneurysm, x-ray diagnosis used for confirmation falls afoul of the problem of the mediastinal mass. The nonpulsating aneurysm is mistaken repeatedly for tumor. Here the therapeutic test, properly conducted, by resolving the peri-aortitis, perhaps, and freeing the aneurysm has, in the writer's experience, made possible

the revision of a diagnosis of tumor of the mediastinum within six weeks in 6 out of 19 cases in which this question was raised.

The electrocardiogram cannot be regarded as a diagnostic implement in the recognition of cardiovascular syphilis as such. On the other hand, this negative statement must not be allowed to minimize for a moment the importance of the electrocardiogram in the determination of the extent of myocardial damage in connection with the problems of treatment and prognosis.

Fundamental Principles of Treatment of Cardiovascular Syphilis.

—The fact that syphilis of the heart and great vessels is thought of less as syphilis than as heart disease is the source of many mistakes in treatment. It is therefore necessary at the outset to recall certain fundamental principles of the treatment of syphilis as a disease which govern the treatment of syphilis as applied to its lesions in the cardiovascular system. First, let it be recalled that syphilis contributes unfavorably to practically all pathologic processes and accordingly treatment for syphilis is indicated in cardiovascular disease, whether the syphilis seems causative or merely coincidental. The weight of this dictum in pulmonary disease is gradually achieving recognition and in time probably equal importance will be attached to it even in the management of the decompensated heart, in which the clinician too often ignores the syphilis while he prescribes rest, sedatives, and digitalis. The possible failure of such general measures to restore a heart until appropriate treatment for the syphilitic infection has been instituted has been demonstrated in individual cases.

It is essential for one called upon to treat cardiovascular syphilis to recall and to make himself familiar with the previous discussions of therapeutic shock and therapeutic paradox, for the cardiovascular mechanism rivals syphilis of the liver as the ideal field for complications of these types. Focal flare-ups of the syphilitic process in the cardiovascular system, with, for example, accompanying edema in a partially occluded coronary artery, a weakened vessel wall or an infiltrated myocardium or conduction mechanism, may produce the gravest results following the first or even several treatments with the shock-producing drug. Cause and effect in the therapeutic paradox are a little less spectacularly traced in syphilis of the cardiovascular mechanism than in syphilis of the liver. It is none the less possible, the writer believes, to prove with reasonable clearness the not infrequent unfavorable outcome which follows the rapid and fibrotic type of healing induced especially by the arsphenamines. It is a notable fact that rapid symptomatic response in syphilitic cardiovascular disease may be positively dangerous and that a patient who is up and about or returning to work in six weeks may be quite unnecessarily dead in six months as a result of his therapeutic miracle. The making of haste slowly by selection of methods which avoid rapid myocardial and coronary fibrosis is a fundamental principle in the management of syphilitic heart disease.

Paradoxical Increase of Signs.—An extension, still on somewhat theoretical grounds, to be sure, but very plausible, of the principle of therapeutic paradox concerns the so-called paradoxical exaggeration of signs with improvement of the patient's condition in early aortic lesions. For example, a diastolic murmur and transient slight dilatation with edema and dyspnea, followed by hypertrophy and restoration of compensation, may result from the initiation of treatment in a patient who,

at the outset, presented only a systolic murmur in the aortic distribution. The roughening and shrinkage of the valve flaps with the actual development of a slight degree of regurgitation in the process of healing seems a reasonable hypothesis not to be interpreted as a therapeutic failure, but probably as a treatment success.

Myocardial and Coronary Factors.—All treatment of cardiovascular, as indeed of all late, syphilis should be preceded by an appraisal of the patient's condition and resources, mental, physical, material. The weak spots in the treatment of cardiovascular syphilis are the myocardium and the coronaries. They, more than any other structure, limit the choice of treatment agents, affect the prognosis. In appraising the myocardial situation, electrocardiographic studies are essential in addition to the experienced appraisal of the functional capacity of the heart muscle. There is no such thing as a distinctive syphilitic electrocardiogram, of course, but there is important information to be gained as to the status of the syphilitic patient's heart from this examination. **Patients with inverted T waves in lead I, and with markedly aberrant QRS complexes are apt to be hastened to their death by the arsphenamines.** Prolongation of life and avoidance of discredit for anti-syphilitic treatment as applied to the cardiovascular system would follow the use of slower-acting drugs and nonintensive methods in such cases.

Patients with syphilitic cardiovascular disease who present anginoid symptoms including paroxysmal pain in the precordial region, vise-like and gripping and referred into the left arm particularly, are candidates for most careful study before treatment is begun. While they may respond quickly by relief of pain and temporarily increased exercise tolerance, too often the early use of an arsphenamine or even bismuth in such cases is followed by a return of obstinate and intractable angina accompanied by increasing myocardial insufficiency and comparatively early invalidism and death. Therapeutic shock is particularly serious in these patients and often quite unpredictable, for autopsy often shows a degree of coronary obliteration out of all proportion to that anticipated from the symptomatology. It follows, therefore, that the detection of evidence of coronary disease is a signal for avoiding therapeutic shock and paradox by long and cautious preparation with iodide and mercury or by really minute doses of the arsphenamines if they are employed at the outset at all.

The tissue reserve of the syphilitic cardiovascular patient must be carefully appraised. Here age, while not an infallible, may be a helpful guide. The patient who finally, in his fifties, goes to the wall with a decompensated syphilitic heart has very little recuperative power. Much less can be expected of him in the way of treatment response than of the younger patient whose aortic murmur and evidence of syphilis are discovered while his heart muscle is still, perhaps, far from exhausted.

Appraisal of Treatment Tolerance.—Closely related to the foregoing consideration is the appraisal of the patient's probable tolerance of treatment and the order of importance of his symptoms. The patient in whose cardiac syndrome there is a marked element of renal insufficiency will tolerate a properly selected arsphenamine better than mercury or perhaps even bismuth, though one of bismuth's great superiorities is, of course, its comparative lack of renal irritative effects. The not uncommon coincidence of neurosyphilis and cardiovascular syphilis just

mentioned demands, first, that pyrexial therapy shall not be used in the treatment of the coincident neurosyphilis; that the management of the cardiovascular lesion shall take precedence; and that the treatment selected shall be such as will not embarrass the circulatory system, or lead to therapeutic shock and paradox in its involved structures. Cardiovascular damage is, in general, much the more serious and irremediable and life-shortening of the two types. In patients who present a coincidence of cardiovascular and visceral lesions as in hepatitis, the indications for the avoidance of treatment complications are much the same for both.

Selection of Treatment.—Arsphenamines.—It is a safe general statement that the arsphenamines (except in very small doses or as bismuth arsphenamine sulphonate) should not be used at the outset in the treatment of cardiovascular syphilis. By delaying their use until a patient has been thoroughly prepared by a slower-acting drug, or by initiating treatment with very small doses, very gradually increased, it is possible to reduce greatly the disadvantages of these drugs, while retaining many of the advantages. If properly used most cases of cardiovascular syphilis can tolerate and be helped by an arsphenamine skilfully selected and administered. The earlier the case and the freer of coronary and myocardial impairment, the more tolerant is it of the arsphenamines and the more advantages are to be gained from their use. The patient should be prepared by from several weeks to several months' treatment with a heavy metal, preferably mercury together with an iodide. The technic of this procedure as applied to this aspect of syphilis is considered under mercury and bismuth. Original arsphenamine ("606") is usable only in the preventive phase of cardiovascular disease, when only the earliest signs have appeared. Invaluable though it is, as I have said, the technic of its administration is too difficult for the average practitioner. The dumping of too much hypotonic fluid into the circulation and the tendency to vascular reactions such as the nitritoid crisis and to gastro-intestinal reactions is too great to make it safe for the average case. **Neoarsphenamine** is, therefore, the preferred drug, and if the maximum dosage of 0.45 to 0.6 Gm. be only rarely exceeded even in adult males and the initial doses kept between 0.025 and 0.1 Gm., it gives most of the good effects to be expected of an arsphenamine, especially when suitably combined with bismuth. Sulpharsphenamine has the distinct advantage of being usable intramuscularly (there is no excuse for its intravenous use), and hence of being available in the occasional technically difficult case, as well as being somewhat freer from therapeutic shock effects. Its disadvantages have been mentioned. **Bismuth arsphenamine sulphonate** in five years' use has impressed the writer as the most eligible of all the group for the treatment of all but the earliest cases of cardiovascular syphilis. The fact that it is a chemical combination with bismuth simplifies treatment while enhancing the effect and doing away with the necessity for preparation with mercury and iodide. The following results secured with bismarsen may be taken as fairly equivalent to and representative of good cardiovascular results in favorable cases as secured by the more complicated methods involving preparation with heavy metals. The Wassermann reaction when positive at the start becomes negative in about half the cases after 15 to 30 weeks of treatment. Of 14 cases observed from two to three years, early marked improvement was ob-

tained in 71 per cent, and this improvement persisted in 64 per cent, indicating a low incidence of therapeutic paradox, in which the improvement would be high at the start, but low after a period of observation. In dealing with individual symptoms in 30 cases, 15 treated by bismarsen alone and 15 by other arsphenamines with heavy metals, both technics proved equally effective; 100 per cent were relieved of pain; 50 to 75 per cent of dyspnea; 65 to 100 per cent of cough; practically 100 per cent of edema, and nearly all of palpitation. Two of 4 decompensated cases were returned to full work. Of 16 completely examined patients, 4 developed the paradoxical slight accentuation of signs with improvement in condition spoken of already as an evidence of healing effect. Results such as these should be obtainable by any careful technic combining heavy metal preparation and an arsphenamine, applied to cases selected for the comparatively good condition of their myocardiums and coronary vessels. That they can be obtained by bismuth arsphenamine sulphionate alone is of course an argument in favor of this drug. Bismuth arsphenamine sulphionate when thus employed should be given in an unbroken series of from 40 to 80 intramuscular injections, the first 10 of which are at three to five day intervals, the later injections five to seven days. The initial dose is 0.025 Gm. (0.375 Gr.) intramuscularly, increasing gradually to 0.1 Gm. (1.5 Gr.) in 10 to 20 injections. The remaining injections are increased quickly to 0.2 Gm. (3 Gr.), the full adult dose, which is then continued throughout the remainder of the series. There seems to be no limit to the tolerance of the drug in all but occasional patients, and the tonic effect is marked.

Mercury in Cardiovascular Syphilis.—Mercury, while it practically never gives rise to significant therapeutic shock effects, does not, *ipso facto*, constitute adequate treatment for early cardiovascular syphilis in which there is hope for arrest of the disease. Mercury by mouth, in particular, is only allowable in the late cardiovascular "wreck" whose myocardial and coronary involvement is such that nothing more effective can be tolerated, or as interim rest treatment in patients receiving courses of more intensive treatment. Mercury by inunction is a satisfactory use of the drug either alone or as a preparation for later arsphenamine treatment. Among the disadvantages of mercury in cardiovascular disease must be included a certain amount of depressing and hemolytic effect, especially serious in anemic patients. The bed patient probably gets the best effect from it. Clinicians dealing with the heart too often forget that the inunction is a very slow method of putting a patient under antisyphilitic medication and that it scarcely begins to take effect within two or three weeks after it is begun. Accordingly, some weeks or even several months of inunctions may be needed for an adequate preparation for either bismuth or the arsphenamines used intensively for curative effect. For this reason, particularly in the decompensated syphilitic heart, the use of a soluble mercurial salt intramuscularly is much more effective than the inunction. After digitalis and general measures have failed, I have known $\frac{1}{4}$ (Gr. (0.01 Gm.) of **succinimide of mercury**, daily, or $\frac{1}{4}$ (Gr. (0.016 Gm.) intramuscularly on alternate days, to produce a rapid improvement. The insoluble salts of mercury given intramuscularly have lost ground since the advent of bismuth, and need rarely be used.

Bismuth in Cardiovascular Syphilis.—The evaluation of bismuth in the treatment of cardiovascular syphilis cannot as yet be regarded as complete. The drug is more rapid in action and more shock-producing than mercury, and less so than the arsphenamines. Many cardiovascular cases will undoubtedly tolerate it in full therapeutic doses from the start, but the writer has witnessed three deaths in rapid succession that seemed due to its employment in cases in which shock might occur, and has also witnessed decompensation develop during its use in ambulant cases without other explanation. He believes, therefore, that except in those patients obviously able to carry a full treatment régime from the start, preparation of the patient with mercury and iodide, or extreme caution in the dosage of bismuth is essential if one would keep his morbidity and mortality at the lowest possible figure. Not more than 0.025 Gm. (0.375 Gr.) of a preparation averaging 50 to 60 per cent metallic bismuth should be given in the first half-dozen injections. Insoluble bismuth salts should be given at four- to seven-day intervals, soluble salts two to three times a week. Bismuth makes an excellent combination with arsphenamine therapy, and greatly enhances the effect of neoarsphenamine without increasing toxic effects. **Neoarsphenamine**, 0.3 Gm. to 0.45 Gm., intravenously can be given simultaneously with 0.1 Gm. (1.5 Gr.) intramuscularly of a preparation containing 50 to 60 per cent **metallic bismuth**, such as the tartrobismuthate of potassium or bismuth salicylate, to any patient whose condition is such that he can carry the neoarsphenamine alone. The combination of bismuth and an arsphenamine in bismarsen, as already described, is accordingly a highly rational one.

Neither bismuth nor mercury in any form should be given intravenously to patients with cardiovascular disease. The toxic dose is too near the therapeutically effective dose by this route, and the need for time-saving can be met satisfactorily by the use of a **soluble salt intramuscularly**.

The iodides have great value in all forms of cardiovascular syphilis. If long-range constitutional effects are sought, doses of 5 to 10 Gr. (0.33–0.66 Gm.) of **sodium or potassium iodide** three times a day may be employed, but for the resolution of peri-aortitis and in vascular syphilis of the brain and cord much larger doses, ranging from 30 to 100 Gr. (2–6.66 Gm.) of the drug, two or three times daily are desirable. The digestive disturbance, coryza and rash are rarely disturbing factors if the drug is given (1) just before meals; (2) in water, not milk; (3) in a concentration of 8 oz. (240 cc.) of water to reach 50 Gr. (3.33 Gm.) or less; (4) and if the larger doses are begun from the outset and not reached by way of a minute initial dose and subsequent one-grain accretions. There is no object whatever in giving the patient with cardiovascular syphilis sodium iodide intravenously. The organic iodine preparations, such as **siomine**, may occasionally be better tolerated than sodium and potassium iodide and a certain amount of iodine effect may be obtained from preparations containing **quinine iodobismuthate** for intramuscular use. The writer has seen no clinical evidence of the increased toxicity of potassium as compared with sodium iodide in syphilitic cardiovascular disease.

General Treatment Measures in Cardiovascular Syphilis.—It is of course as important to emphasize to the practitioner and the syphilologist that the syphilitic with a heart complication must be managed as a heart case, as to remind the cardiologist and internist that the syphil-

itic cardiovascular patient has syphilis. The digitalization and the management of decompensation of the syphilitic heart should be supervised by one familiar with the general principles. Rest should not only be employed in the advanced case, but it should be made available, or activity should at least be curtailed, in the patient with aortitis with valvular involvement while the adjustments in heart load due to shrinkage of healing valves are taking place. This is usually during the first six weeks to six months of treatment. The great importance of integrity of the aortic valve in the future of the patient is very apparent in comparing the behavior under treatment of aneurysm and aortic regurgitation. Too much care cannot be taken to insure a slow healing process as compared with a rapid fibrosis and shrinkage with coronary orifice constriction. The securing of rest for the syphilitic heart is sometimes rendered difficult by the wreckage of the patient's morale on the familial, social, and stigmatic aspects of his condition. Time spent, therefore, in adjusting the patient's viewpoint may be as important as drug therapy. **Occupational therapy** and **progressive relaxation** are very helpful. There are no incompatibilities between the sedatives usually employed and any form of antisymphilitic medication. The tonic effect of arsenical treatment sometimes encourages undesirable gains in weight that must be watched. Relief of pain in patients with repeated anginal seizures sometimes becomes a critical matter, and the **Jonesc6**¹⁷⁴ **operations** upon the cervical sympathetic are therefore justified for the control of this particular phase of the problem. There is no more inveterate relapser than the once decompensated aortic regurgitant patient, and permanent adjustments of future activity to the lowest possible terms must be made from the very start—if possible, before rather than after the first breach of compensation has developed. In water-logged cases, the diuretic effect of **novasurol** and **soluble bismuth salts** such as sodium bismuth tartrate previously mentioned in connection with hepatic syphilis may be kept in mind.

Special Considerations—Aortitis and Aneurysm.—In a phase of syphilis in which the keynote should be individualization, it is difficult to propose a system of treatment. It may be suggested, however, that in a patient with competent valves and no aneurysmal dilatation, a course of 40 to 60 **inunctions** or 20 to 30 **mercuric succinimide injections** (never an arsphenamine at the start, unless minute doses of neoarsphenamine or the above-described course of bismarsen) may be followed by 12 to 15 injections of an **insoluble bismuth preparation**, and this in turn, without rest period, by a course of 8 to 15 **neoarsphenamine injections** of 0.2 to 0.6 Gm. Alternate courses of bismuth, 10 to 12 injections, and neoarsphenamine, 8 to 10 injections, may be employed to a total of three courses of each type, depending on the tolerance and response. It is also possible to give the bismuth and neoarsphenamine simultaneously, at weekly intervals as above described. The iodide therapy at the start may be continued for some time after the cessation of other treatment in periods of two months on and two off. Only in young persons, in excellent condition, should original arsphenamine be used in the effort to stop the process entirely. That this arrest is by no means easy is evident from the fact that patients may in the first five years of a syphilitic infection go on to the development of an aortitis in spite of and in fact during intensive antisymphilitic treatment. While it is desirable to reverse the blood Wassermann reaction, especially in the

earlier cases, it is not justifiable to overtreat the advanced cardiovascular patient in the effort to secure a negative. Much of the best judgment required of the physician in the management of these patients is exercised, especially in their later years, in not doing too much. Life-long observation is, of course, an absolute essential in all cases. The management of early aneurysm may be intensive, after a period of careful preparation has insured the establishing of therapeutic effect without enlarging the lesion or weakening the vessel wall. An injudiciously treated aneurysm may rupture after the first arsphenamine treatment. Very occasionally an aneurysm will reduce in size under treatment, but more often it enlarges as the peri-aortitis resolves itself, and comes to a stationary condition in which it will remain for years without further change if the patient keeps his activities within bounds. During this period of stable equilibrium treatment should be pushed to meet whatever syphilitic complications there may be, and to try to stop the process in the vessel wall. Surgical intervention and the wiring of aneurysms may be considered in rare cases of very large eroding sacs.

The writer's advocacy of the therapeutic test in suspected cardiovascular syphilis needs some qualifying conditions. Provocative tests are theoretically rather risky and should be discouraged if there seems the slightest risk of shock or paradox. A series of serologic tests after a short course of non-shock-producing treatment is better. At times as already stated the use of the therapeutic test in mediastinal masses is of importance in identifying aneurysm by the development of pulsation in what appears, under the fluoroscope at the outset, to be a solid tumor. For such therapeutic tests, the soluble mercurial salt and iodide followed by bismuth is safer than the initial administration of arsphenamine. Not less than six to twelve weeks should be allowed for the resolution of the peri-aortitis to the point which permits pulsation to appear.

Treatment in Cases of Coronary Sclerosis and Advanced Myocarditis.—If the degree of damage seems considerable or the symptoms clear-cut, it is, the writer believes, dangerous to subject lesions of this type to an arsphenamine therapy until after several months of preparation, if at all. The occasional brilliant exception does not offset the high proportion of such cases which, in exchange for a temporary slight gain, months after when the connection with the previous intensive treatment has been lost sight of, pay the price of rapidly failing hearts. While the outlook of such cases is at best poor, the younger patients sometimes furnish encouraging exceptions, and after careful preparation can stand the rigors of a course of treatment which at least controls their anginas, though I have seen no examples of electrocardiographic change for the better. In older patients, iodide and rest seem the best resorts, and if not overtreated the life duration achieved may sometimes quite outrun expectancy.

Peripheral Vascular Disease Accompanying Syphilis.—It is out of the ordinary to see peripheral vascular disease in patients with syphilis exhibit more than equivocal therapeutic results. It is true, however, that hypertension in the syphilitic patient sometimes undergoes marked and apparently lasting reductions under treatment with the arsphenamines. The nature of essential hypertension being so much in dispute, and apparently so rarely syphilitic, the source of these good effects must remain in question. In general it may be said that the hypertensive patients tolerate treatment with the arsphenamines in moderate doses

quite well, but carry the heavy metals, especially mercury, with more difficulty. The combination of bismuth and an arsphenamine, either as in bismarsen or in the combined neocarsphenamine-bismuth course already described, is probably the best available.

Enderteritic processes with gangrene and examples of thromboangiitis obliterans accompanied by positive blood serologic tests for syphilis do not furnish a very satisfying field for syphilotherapy. Almost any form of treatment for syphilis may produce a transient improvement, perhaps nonspecific in origin, only to be followed by relapse and progression on which further treatment for syphilis has little or no influence. There are, however, no actual contra-indications to an intelligently directed therapeutic test if the Wassermann reaction is positive.

Preventive Aspects.—The treatment of cardiovascular syphilis like that of neurosyphilis is, let it be reemphasized, undertaken years too late. Without means of accurately diagnosing cardiovascular syphilis early in its course, and even without absolute assurance that modern treatment pushed to its utmost can prevent the progress of the disease once the aorta and heart muscle are involved, we can cherish only the hope that identification of a syphilitic infection in the sero-negative primary stage before the disease may be supposed to have gained its visceral and vascular foothold, will protect the patient from syphilitic cardiovascular disease.

It rests with the practicing physician who sees the patient when he presents himself with his chancre and before the appearance of his secondaries essentially to modify the relatively discouraging situation with respect to cardiovascular syphilis today. By the intelligent and vigorous use of arsphenamine and mercury or bismuth during the sero-negative primary stage in long courses without rest intervals and without regard to the first or subsequent negative Wassermann tests, the practitioner may attack cardiovascular syphilis at its root. The rational treatment of cardiovascular syphilis today is the intensive and thoroughgoing treatment of primary and secondary syphilis.

SPECIAL DIAGNOSIS AND TREATMENT OF NEUROSYPHILIS

No disease illustrates better than syphilis the need for a shift of viewpoint in the training and practice of physicians, from consequences to forerunners, from remedial to preventive measures, from the late and obvious signs to the still, small and obscure beginnings of disease processes. In the control of neurosyphilis this issue is critical and upon it rests the whole future of this phase of the campaign against the disease. Instead of teaching neurosyphilis to the medical student, as tabes and paresis, it must be taught to him in an anticipatory way, as a percentage factor in all cases of syphilis seen in the primary and secondary stages, as an occult and symptomless affair, detectable only if search be made for it, and recognized then only by procedures which have had relatively little currency in the past and which form an unwelcome but unavoidable addition to the technical problems of managing the disease from the very first day of its onset. This refers, of course, to the more intensive methods of treating syphilis and to the spinal fluid examination as the most important means of detecting neurosyphilis in its period of greatest responsiveness to treatment.

Treatability in neurosyphilis is a function of the time at which the

complication is recognized and effective measures begun. Neurosyphilis, as it has been known heretofore, is largely a controllable aspect of the disease, even today. It can now be all but extinguished by a determined effort on the part of the practitioner and a full utilization of the diagnostic and therapeutic resources against it. If cerebrospinal syphilis, tabes and paresis occupy the same relation to the general mortality and morbidity of syphilis fifty years from now that they do today, the fact will mark the failure of teachers of syphilology to reach their goal, and of the practitioner of everyday medicine to measure up to his responsibilities.

The outstanding facts about neurosyphilis that apply to the work of the practicing physician may be summarized as follows: Involvement of the nervous system is not a late consequence but a very present and immediate fact in 25 to 30 per cent of patients who present themselves with the disease. In all probability, all patients who acquire syphilis suffer some invasion of the nervous system while, to follow Belote's phrase,¹⁷⁵ only a part show involvement or, to use the writer's phrase, react to it. One patient in four will develop important neurosyphilis; one in ten will develop serious neurosyphilis; and one in twenty will develop refractory or even fatal neurosyphilis, even under vigorous treatment. The decision as to whether the nervous system is involved or will be involved in a given case can never be conclusive or final. While reaction shows itself in the spinal fluid examination in a large proportion of cases, there will always be some who will present true neurosyphilitic complication with negative spinal fluids and negative blood serologic tests. These will include especially the vascular accidents, preponderating early, and the slow, degenerative cord lesions and localized gummatous changes late in the disease. Early syphilis is preponderantly meningeal in character and the increased cell count in the spinal fluid stands first as a warning of its presence. Of what use, then, is a spinal fluid examination in which, as often happens, only the Wassermann test is requested or reported? For the positive Wassermann reaction in a spinal fluid is a later, not an early sign. Most meningeal neurosyphilis yields to treatment, and 90 per cent of it can be controlled by intensive measures.¹⁷⁶ A simple routine of prolonged and careful treatment of the early infection with **arsphenamine, bismuth and the iodides** in accordance with the procedures outlined in previous sections of this presentation disposes of all but perhaps 20 per cent of neurosyphilitic involvement. Half of the remainder requires hammering and special methods. Two per cent of the resistant 5 per cent yield to extreme measures; 3 per cent probably will not respond at all.

Certain early general warnings that neurosyphilis is to be an important problem in a particular case should be reemphasized. *First* of all, the presence of even slight abnormalities in the course of the blood serologic tests toward negative and in the findings in the spinal fluid should arouse suspicion. *Second*, the recurrence of transient partial positives in the Wassermann curve of an early case, or of conflicting reports where both Wassermann and precipitation tests are done, should lead to closer observation and further study. *Third*, too early development of a negative serologic test should put one on guard as indicating a relapsing tendency (Moore and Kemp¹⁷⁷). *Fourth*, a fixed positive or a relapsing positive blood serologic test should never be simply repeated and repeated during a period of rest from treatment. It should be amplified at once by a spinal fluid examination. *Fifth*, the slight

rise in cell count in a spinal fluid which is otherwise negative is very important. *Sixth*, if, however, a patient is carrying a full program of effective treatment, the spinal fluid examination may be deferred at least until the end of the first six months and perhaps even as late as the first year. *Seventh*, it is a fundamental principle that no patient with early syphilis is to be placed on a complete rest interval or a relatively ineffective form of treatment, such as mercury by mouth, until a spinal fluid examination has been had. Failure to regard this precaution leads to many examples of neurorecurrence. *Eighth*, the question as to whether a negative spinal fluid examination, even at the end of a full and intensive course of treatment, proves the patient to be free of danger from neurosyphilis can be answered only by qualified assurance. It is unlikely that a patient who has had a completely negative spinal fluid examination under such circumstances will in the future develop neurosyphilitic lesions. On the other hand, it is by no means certain that he will not.

Vigorous reëmphasis should be placed on the fact that negative blood serologic tests, no matter how often repeated, do not prove the absence of neurosyphilis in patients with early or late manifestations. Fixed positive serologic tests and the relapsing positives, including repeated relapses on either side of a two-phase test like the Wassermann-Kahn combination, may result from a neurosyphilitic involvement and necessitate a spinal fluid examination. The repeatedly negative blood Wassermann reaction is thus absolutely unreliable as a guide to the cessation of treatment in an early case, and in trusting it the practitioner of today makes one of his most serious mistakes in the management of early syphilis from the standpoint of preventing neurosyphilis.

Having now thoroughly stressed the fact that the spinal fluid examination, completely and properly performed, may furnish the sole clue to the presence of a neurosyphilitic involvement, an account should be given of the general symptomatology of neurosyphilis. The chronology of the disease of course necessitates that early neurosyphilis shall pass from an asymptomatic stage to one in which symptoms are somewhat more conspicuous than signs; then to one in which signs and symptoms parallel each other, and finally to a stage in which signs assume the upper hand. Thus it may be stated that in the aggregate the neurosyphilitics who are up and about present signs three times as often as they do subjective symptoms. This necessitates thorough-going objective approach to the patient if the maximum amount of neurosyphilis in ordinary practice is to be recognized. Dividing the course of neurosyphilis on a chronologic basis, the following may be offered as a summary.

Symptoms and Signs of the First to the Fifth Year.—*The symptoms* include headaches and head pains accompanying alopecia and leukoderma; ringing ears and dizziness; impaired vision; other symptoms of cranial nerve lesions (diplopia, deafness, facial palsy); neurasthenoid symptoms (nervousness, lassitude, malaise and pains, phobias, emotional disturbances and insomnia). Early hemiplegia and epileptiform convulsions are also noted in this period. *The signs* of the first to the fifth year include, in addition to the fixed or relapsing serologic tests and the spinal fluid findings, the presence of pupillary irregularity, especially anisocoria and disturbed light and accommodative reflexes; fundus signs of involvement of the second nerve, including papillitis, neuroretinitis, early disk pallor and so forth; disturbed reflexes, usually accentuated;

and cranial nerve lesions, including ocular paralyses, facial palsy, deafness, or impaired hearing, reduced bone conduction and so forth.

Symptoms and Signs of the Fifth to Tenth Year.—*The symptoms* include headache and head pain, stomach trouble, backache, neuralgias (or root pain); cerebral neurasthenia (including tremor, fatigability, irritability, insomnia and memory loss); seizures and spells (aphasic, epileptiform, apoplectiform, hemiplegic); paresthesias (prickling, numbness, burning, tingling). *The signs* of this period include again the spinal fluid findings; pupils (irregular, unequal or slow); isolated paralyses and pareses; lower-cord reflexes (diminution and loss or early accentuation and spastic changes); early sensory changes (widespread reduction in pain, bone and muscle joint senses); alterations of personality.

Symptoms and Signs of the Tenth to Twentieth Year.—*The symptoms* include reduced libido and potentia; difficulty in urination; ataxia, noticed first after dark; failing vision; diplopia and ptosis; lightning pains; girdle sensation and other paresthesias; visceral crises; seizures or attacks; mental symptoms; cardiovascular symptoms. *The signs* include Argyll Robertson pupils, anisocoria, mydriasis, miosis; the Romberg or Babinski and spastic signs; optic atrophy (primary); extra-ocular palsies; lost lower-cord reflexes; hemiplegias and hemipareses; dysarthria and aphasia; grandiose and paranoid delusions; conduct slump; trophic joints and spontaneous fractures; mal perforans.

Symptoms and Signs of the Twentieth to the Fortieth Year.—*The symptoms* include advanced ataxia or paraplegia, severe paresthesias and pain; tabetic infected bladder with cystitis; attacks of fever (pyelitis); uremic symptoms; advanced mental deterioration; arteriosclerotic changes; apoplexy. *The signs* include, of course, further progression of the foregoing with rising blood urea and declining renal function.

Such a summary as the foregoing must be read, of course, with the realization that some neurosyphilitic pictures lack specificity and that not all neurologic symptoms in the course of syphilis are due to syphilis of the nervous system. An examination of the spinal fluid usually but not always clarifies the diagnosis. In some cases a therapeutic test is a final resort and even here, as in multiple sclerosis and glioma, nonspecific therapeutic response makes this procedure of uncertain value. The summary is, however, a fair representation of the neurosyphilology of ordinary medical practice. The unfolding of the picture may be stopped at any point by the arrest of the disease, or accelerated so that the symptoms of the last decade may furnish the closing episodes of the first.

In order to arrange the subjective symptoms and objective signs of preponderantly late neurosyphilis in order of frequency, the following table is presented (after Stokes and Brehmer, 200 cases¹⁷⁸).

<i>Subjective Symptoms in Preponderantly Late Neurosyphilis</i>	<i>Per Cent</i>
Gastric symptoms	25
Lightning pains	16
Headache and head pain	15
Diplopia and failing vision	13
Malaise, weakness	10
"Rheumatism"	10
Bladder symptoms (subjective)	9
Loss of consciousness	9
Girdle pain	8
Ataxia (subjective)	8
Dizziness	8

<i>Objective Signs in Preponderantly Late Neurosyphilis</i>	<i>Per Cent</i>
Abnormal knee reflexes	73
Abnormal Achilles reflexes	67
Abnormal pupillary reflexes, muscular paralyses or fundus changes	63
Sensory disturbances	49
Romberg positive	43
Mental symptoms	39
Ataxia (objective)	38
Argyll Robertson pupils	35
Bladder abnormality (sphincter and atony)	32
Speech defect	14

<i>Eye Findings in Neurosyphilis (Stokes and Brehmer—126 Cases)</i>	<i>Per Cent</i>
Total presenting pathologic eye findings	63
Argyll Robertson pupils	35
"Slow" reflexes	23
Irregular pupils	19
Fundus changes	15
Muscular paralyses	12

Clinical Examination for Neurosyphilitic Involvement.—One of the most important elements in the control of neurosyphilitic complications in any given patient with syphilis and, of course, the detection of such involvement when present, is a systematic habit of examination. It seems worth while to include here a routine for this base-line examination which can serve as an office guide for syphilologic examination in general. It should be understood that the items in the examination of the nervous system here included do not constitute by any means a complete neurologic examination or one upon which an absolute diagnosis can necessarily be based. An examination such as this serves to identify the presence of changes which may be neurosyphilitic but which in the presence of doubtful or conflicting evidence must be evaluated as a whole by an expert and particularly, in certain cases, a neurologist.

Itemized Examination of the Nervous System for Routine Purposes.—

1. Inspection of the patient for atrophy, trophic changes, functional disorders.

2. *Eyes.* Pupillary reaction to accommodation and light, direct and consensual; extra-ocular movements; ptosis; nystagmus; visual acuity (rough test with type); visual fields (rough).

3. *Ears.* Watch test.

4. *Seventh nerve.* Whistle, wink and grin.

5. *Deep reflexes.* Biceps, triceps, knee, Achilles (taken kneeling), umbilical, cremaster.

6. *Motor function.* Extension, flexion, arms and legs against resistance.

7. *Coördination test.* Finger to nose, heel to knee, adiadokokinesis.

8. *Spasticity test.* Babinski, ankle clonus.

9. *Test of motion and position.* Romberg, gait, and orientation of great toe.

10. *Sensory tests.* Vibration sense with the C-128 fork over the malleoli and olecranon processes; differentiation of pin point and touch over the extremities and trunk, cheeks and forehead.

11. *Speech tests.* Handwriting tests and mentality tests (memory, etc.).

Certain practical points with reference to the items of this examination deserve special mention. Pupillary tests should be performed either in the dark room or by a frontal illumination rather than one coming from the side which may produce false impressions of slight inequality. It is important to provide for distant vision in testing accommodation. Reflexes should be interpreted in terms of the general tone of the individual skeletal and nervous systems and not accepted too readily as exaggerated or reduced on the basis of isolated tests. The Achilles reflexes, in the writer's experiences, are best tested with the patient kneeling. The extremely nervous patient may be detected in the unconscious act of "holding" a reflex and similarly the very alert patient in repeated examinations becomes proficient and vitiates the value of such tests as the Romberg and study of the gait. Tests involving sensory discrimination are affected by mentality quite as much as by actual local sensory changes and careful discrimination is sometimes necessary. While a neurologist would find many items which he would conceive to be important omitted from the foregoing office routine, some regard is necessary therein for the limitations of the average physician's time.

Pains, Paresthesias, Genito-urinary Symptoms.—A certain amount of special emphasis deserves to be placed upon the pains and paresthesias of late neurosyphilis and upon disturbances of bladder control and of the sexual reflexes. Both these groups are very important as suspicion-arousers, and receive too little attention in the ordinary inquiry into symptoms. The typical lightning pain is sharp, stabbing, spot-like, and may recur again and again in the same place, often singling out a spot such as the heel or the instep for repeated shocks. The pains may also come in showers over a considerable area, leaving the skin tender to touch for some hours or days after the shower subsides. There is no aching quality to the pain, no tenderness to pressure, no accentuation with movement as in myositis and myalgia, and no prickling, numbness or burning as in neuritis. Accentuation with fatigue and unfavorable weather changes and with the onset of infections is the rule, and probably helps as much as anything to bring about the common diagnostic misinterpretation of rheumatism. Disturbances of bladder control were found by Ockerblad¹⁷⁹ to be present in 30 per cent of tabetics and 80 per cent were found to have bladder symptoms. The aid of the urologist in the recognition of the condition of the bladder ("cord bladder") is very important and sometimes helpful in early diagnosis. Bladder symptoms and loss of libido and potentia rank with lightning pains among the very earliest symptoms of spinal cord syphilis. The onset of the bladder symptoms may be so insidious that the patient is entirely unaware of the developing atony of the bladder musculature. He believes himself to be emptying the bladder completely when in reality a residual urine of 100 to 500 cc. may be present. The first warning of trouble comes when the patient wets the bed at night from overflow through a spastic sphincter from a distended bladder. "Hard to start" is the phrase most patients use to express the difficulty of relaxing the sphincter and emptying the bladder by its own contractility in the earlier irritative phase. Dribbling after a supposed complete evacuation indicates either sphincter atony or a retention of urine in an atonic

distended bladder. The physician has an unmistakable responsibility in detecting these cases and the repeated catheterization of a patient without an examination of his reflexes and a search for other neurologic signs of syphilis is inexcusable.

Pupillary Changes.—Pupillary changes being among the most important early signs of neurosyphilitic involvement, there is a strong temptation to insist that marked irregularity of the pupils, sluggishness or an outright loss of light reflex with preservation of accommodation is pathognomonic of neurosyphilis. The value of pupillary signs in the diagnosis of neurosyphilis must certainly be critically considered in the light of our growing comprehension of arteriosclerotic phenomena and of lethargic encephalitis. None the less, exceptions to the syphilodiagnostic rule are comparatively very rare and it has seemed to the writer safer for the diagnostician to regard pupillary disturbance as presumptive of neurosyphilis and to trace this possibility to the ground by adequate study than to accept too readily the likelihood of occasional exceptions. The authoritative review of this problem by Nonne reaches the same conclusion.

Cerebral Symptoms: Seizures. The symptoms accompanying cerebral syphilis present the same variability and the same not infrequent non-specificity which applies to the discussion of cord symptoms. The seizure or convulsive attack is a very common symptom of all forms of cerebral neurosyphilis and the prodromal or abortive seizure may recur for years before coming to full intensity. On the other hand, the first apoplectic attack may be fatal. The most frequent seizures are epileptiform but there may be incomplete types, including simple "fainting spells," "dizzy spells," and petit mal attacks with various special forms of irritative muscular contraction and temporary speech disorders. The immediate prognosis of the epileptiform seizure in neurosyphilis is good but the recovery is usually short of the degree of functional capacity present prior to the attack, and the cumulative disabilities of a succession of seizures ultimately result, therefore, in severe deterioration and fatal outcome.

The speech disorders of the parietic are fairly characteristic. The aphasia is more serious in proportion as it is fugitive, transient and incomplete. Paradoxically, the more satisfactory the recovery, the more serious the ultimate prognosis. Taken together with the facies, the slurring of words which constitutes the parietic dysarthria makes a combination that is suspicion-arousing on sight. Syphilitic neurasthenia deserves extended comment but is, unfortunately, difficult of definition. Nonne's famous aphorism, "A neurasthenic with syphilis in his history suggests the parietic," is only too easily forgotten and should be controlled by the spinal fluid examination. All too many persons, and particularly physicians, have been allowed to go on to established and gravely degenerative paresis as the sequel of diagnoses of neurosis and overwork in middle life. The items which constitute "conduct slump" in the early diagnosis of paresis arrange themselves with difficulty under any scheme, but expansiveness and euphoria on the one hand, and depression on the other, constitute general categories. An overgrown tendency to enter upon new enterprises at an age when conservatism usually comes to the fore, inability to see obvious obstacles, over-liberal speculative use of resources in the face of existing responsibilities, may be the first warnings of impending trouble. The handwriting signs of

omitted letters and words, and tremor, may be detected in the patient's signature, business correspondence and check-writing. Causeless rages directed against children or animals may early attract attention, although the patient may remain for a long time amenable to reason and repentant after each outburst. The sudden slackening of a previously rigid sexual morale is a very significant symptom. Before diagnosis becomes apparent, the patient may be involved in bigamous marriages. Carelessness in personal appearance, including the spotted waistcoat, often goes with the increased flabbiness of mental and physical tone. A steady loss of weight has been emphasized as an unfavorable prognostic symptom. Persecutory ideas (paranoid state) may, after a considerable period of silent brooding, come suddenly to the front in a single phrase or outburst that may subside again only to take form months later in some well directed attack upon an object. The comparative clearness of the mental background from which explosions may sometimes arise well emphasizes the care that should be taken in releasing from custodial supervision the cerebral syphilitic who has once shown definite signs of persecutory delusions. In taking the history of such patients, indirect evidence from the statements of others should be critically examined with respect to motives, for friends, associates and even marital partners may have personal reasons for prejudiced testimony or may be unduly suggestible. A physician may at times be made the tool of a scheme to secure a power of attorney, the sequestration of a wealthy person or the replacement of a chief by some ambitious and unprincipled subordinate. In critical cases, involving important persons and interests, slowing down of the process of examination to allow time for better acquaintance with the patient himself and a development of his confidence in the examiner may lead to valuable clues and correct mistaken impressions. Much caution must be used in interpreting early mental signs for, as Foster Kennedy among others has well pointed out, the War demonstrated the fact that extreme fatigue alone, to say nothing of disease of the nervous system, may give rise to symptoms indistinguishable from those of early paresis.

Treatment of Early Neurosyphilis.—As in dealing with any important group of structures involved by syphilis, an appraisal of the situation is the first necessity. For purposes of prognostic and therapeutic classification it is convenient to speak of early meningeal neurosyphilis, vascular neurosyphilis and parenchymatous syphilis as three types of involvement which, while not absolute in their definition and frequently combined in varying proportions in a single case, none the less have fairly distinct treatment characteristics. Neurosyphilis at the outset is, as has been said, overwhelmingly meningeal in character. This type of involvement presents itself clinically, of course, in the form of symptoms including particularly those of meningitis of the base of the brain, with involvement of cranial nerves. Serologically, the spinal fluid of early meningeal syphilis is negative to the Wassermann reaction except in the largest amounts; it shows a marked increase in globulin; a marked rise in cell count and, as a rule, a first-zone colloidal test which in this case does not mean paresis because not accompanied by the other fluid findings that make up the typical "red flag" syndrome. Accepting the high cell count as evidence of an active meningeal neurosyphilis, one may, for purposes of practical convenience, though there is no absolute justification for it, regard the positive Wassermann on the spinal fluid

as an expression of parenchymatous change. Vascular neurosyphilis tends to show relatively little evidence of its presence in the spinal fluid examination as such. It is, therefore, the type of neurosyphilis most frequently associated with negative serologic findings when it occurs in comparative purity, as in the syphilitic hemiplegias. Meningo-vasculo-parenchymatous neurosyphilis or, according to the older terminology, cerebrospinal neurosyphilis presents varying grades of positive Wassermann on the fluid, an increase in globulin, a moderate or high cell count, and, as a rule, a second-zone colloidal test. Parenchymatous neurosyphilis tends to present strong and difficultly reversible positive Wassermann tests on all concentrations of the spinal fluid, together with marked increase in globulin, a relatively low or even a normal cell count, and most frequently a first-zone colloidal test though occasionally the second zone may appear. It is, of course, impossible to make these differentiations absolute but it may be said in general that meningeal neurosyphilis is very responsive therapeutically and that 90 per cent of these patients will achieve complete clinical and serologic negativity through persistence in intensive treatment. Meningo-vasculo-parenchymatous neurosyphilis (cerebrospinal) likewise responds very well to persistence in standard intensive measures. Excellent results, both clinical and serologic, may be obtained in 74.5 per cent of cases. Next in order from the prognostic standpoint, under standard treatment, fall the tabetics who, because of the comparatively late and degenerative character of their symptoms and signs, show an excellent response clinically and serologically in only approximately 48.3 per cent of cases. Vascular neurosyphilis responds to standard measures in a still smaller proportion of cases and 38.9 per cent may be expected to achieve good results. The results of treatment of general paresis, either in the preparetic phase of serologic without clinical signs or in clinical paresis as such, constitute the most completely disappointing of all the groups under routine arsphenamine and heavy metal treatment. At most, not more than 1 or 2 per cent of satisfactory results can be expected, and this rule has so much force that the achieving of a satisfactory therapeutic result under arsphenamine, mercury and bismuth treatment, if it be lasting, throws the entire diagnosis into doubt.

Treatment of Early Meningeal Neurosyphilis.—Such a summary as this serves as an excellent rational basis for therapeutic decisions and choices of methods. Early meningeal neurosyphilis, recognized within the first six months of the infection and devoid of any such critical or alarming warning signal as the parietic formula ("red flag"), may be continued on standard intensive treatment; but the writer's experience tends to support the necessity for a change from neoarsphenamine to arsphenamine proper ("606") if the maximum of good effect is to be obtained. If it is decided to continue the treatment of the patient by such methods, a spinal fluid examination at least every third month is a necessity for the determination of a satisfactory degree of progress. It should be specifically mentioned that the statements above made in regard to the effectiveness of standard treatment if continued in cases of early meningeal neurosyphilis do not apply to the continued use of neoarsphenamine by any technic with which the writer is familiar. Particularly is this true of the weekly injection of neoarsphenamine so frequently carried on for months in the attempt to reverse a positive blood Wassermann reaction based upon neurosyphilitic involvement.

The writer has seen series of nearsyphilitic injections, often considerably exceeding a hundred in number, administered to patients with paraparesis or "rod flag" formides on the spinal fluid without the slightest therapeutic effect on either symptoms or serology.

Intensified Treatment Methods.—If, after a pair of standard intensive treatment for an early infection, the patient continues to show spinal fluid abnormalities, even though they may not be those of a clear-cut paraparesis, an intensification of methods beyond that of the ordinary intravenous and intramuscular treatment becomes absolutely imperative. For this intensification three procedures may be considered to be available: intraspinal therapy, tryparsamide, and fever therapy. With respect to intraspinal therapy, a very interesting change has occurred with the advent of tryparsamide and fever. A decade ago the intraspinal use of arsphenamine-d blood serum or arsphenamine-d blood arsenphenamine-d blood serum, after the Salter-Elliott or the Ogden techniques, had achieved a generally recognized place as the therapeutic corner of last resort in neurosyphilis. While by no means universally acceptable, particularly to neurologists, and while modified by such influences as Dorem's advocacy of spinal drainage, the writer's own experience with the method agrees in general with that of Fletcher, Gower, and others in regarding it the most important place in its day in the treatment of refractory neurosyphilis. The results above detailed on the various types of neurosyphilis were obtained in 40 per cent of the total series of cases by the addition of intraspinal therapy to intensive systemic measures. With the advent of tryparsamide and fever therapy, the highly specialized and difficult intraspinal procedure has greatly declined in popularity as a general treatment measure and has been relegated in its more recently published application to the treatment of special conditions such as primary optic atrophy, rapidly progressive tabes, and so forth. In general one may properly welcome this substitution of a simpler treatment technique, such as that with tryparsamide, for example, for the extremely complicated, trying and dangerous only under intraspinal therapy, which under the best circumstances could be made available only to the comparatively few patients who could have the use of experts and treatment centers. With the advent of tryparsamide it becomes possible to treat resistant neurosyphilis under the conditions of general practice. It follows, therefore, that if, after a nearsyphilitic trial of intensified standard treatment for syphilis (including the substitution of arsphenamine for nearsyphilitic), one is not successful in procuring good clinical and serologic results, the present-day choice, in the absence of a special indication for intraspinal therapy such as a localized and resistant or rapidly progressive cranial nerve lesion (nerve II and nerve VIII), lies between tryparsamide and malaria.

Tryparsamide Therapy.—Tryparsamide is gradually developing a widespread, well merited popularity in the treatment of neurosyphilis. As in all forms of treatment for this phase of the disease, its selection as the method of choice must depend upon the individual case more than upon general considerations. It is impossible here to summarize the accumulated literature on the subject, and reference for this purpose may be had to a résumé by Chambers.¹⁹ The summary by Johnson²⁰ is the longest and most extended experience with the drug that is extant. The publications of Solomon and his associates, and of Becker,²¹ previously referred to, also contain much material of importance. The

technic of administration of the drug and for the detection and avoidance of complications is given under Tryparsamide. The following may be offered as a summary of the most important principles involved in the therapeutic use of the drug, drawn from the various sources above mentioned and from the writer's personal experience.

1. Tryparsamide should, at the present time, be limited in its use to the treatment of neurosyphilis and especially of paresis and paralytic.

2. Tryparsamide should not be invoked within a year to 18 months of the onset of a syphilitic infection, except for very special reasons. During this probationary period the patient should be under intensive treatment for the disease as a general infection rather than a local process. Moore and his coworkers¹⁰ have shown conclusively that the drug is entirely ineffective in all other aspects of systemic syphilis except that of the nervous system.

3. Like all forms of neurosyphilotherapy, the results of tryparsamide treatment are best the earlier in the course (after the first six to twelve months) it is employed and the younger the patient who receives it. Lorenz found that in general his good results occurred in patients who were seven years younger than those exhibiting unsatisfactory results. In general, also, the excited rather than the depressed or depressive cases respond well (after the therapeutic shock effect) and achieve the best ultimate results.

4. Tryparsamide produces definite therapeutic shock in patients with clinically recognizable symptoms and signs of cerebral involvement; and this must be provided for in advance. Not infrequently in the treatment of patients with the mildly excited types of paresis a maniacal phase ensues from the fourth to the sixth week after the institution of tryparsamide treatment and special measures or even confinement may be necessary.

5. The effects of tryparsamide in general are tonic and stimulating. Weight gains are to be expected. Certain patients, usually rare exceptions in the earlier cases but becoming more common in the treatment of late involvements, do not tolerate the drug well. When such intolerance appears, it is wiser to stop than to continue. It is quite possible to push late, badly deteriorated cases and even some excited patients to their death. Such reactions are, however, the exception rather than the rule.

6. Tryparsamide should not be given in small doses or for short series. Lorenz particularly cautions against the use of doses less than 1 Gm. (15 Gr.), stating that they are definitely irritative and hasten the progress of the disease. The range of dosage may be taken to lie between 2 and 5 Gm. (30-75 Gr.), with the large majority receiving 3 Gm. (45 Gr.). The total amount of the drug given in successful cases ranged from 48 to 1500 Gm. (720-22,500 Gr.) (Lorenz).

7. All recent observers emphasize the fact that the best clinical and serologic results in tryparsamide do not appear until after 70 to 100 injections. It is a matter not as yet definitely settled whether these should be given in broken courses or continuously, but either technique may be accepted as satisfactory according to the circumstances and individual indications.

8. Tryparsamide treatment is not an exclusive form of therapy. It may be used to advantage in alternation with courses of standard treatment if indicated by the general status of the syphilis or in alterna-

tion with fever therapy or as a sequel to it if indicated by the status of the neurosyphilis. It is also possible to use mercury and bismuth in conjunction with it, and the original Lorenz-Loevenhart technic prescribed the use of mercury salicylate in one-grain doses weekly. In the longer series, of course, this must be broken by rest periods. Particularly in the earlier cases, this combination with other forms of treatment seems desirable.

9. Control examinations of the spinal fluid once every six months in the longer tryparsamide courses are desirable. In the very early cases, where tryparsamide has been selected in preference to fever therapy because of convenience or other circumstances, it may be desirable to re-examine the spinal fluid within three months after the institution of treatment. In general, however, the above given rule with regard to the number of injections necessary before distinctive effects can be observed would call for six months to a year before the serologic response is appraised by spinal fluid examination.

10. Eye complications, the only serious risk associated with the use of tryparsamide, may be expected, under proper control, to occur in less than 2 per cent of cases. Subjective symptoms may appear in from 5 to 7 per cent, objective disturbances in 1 to 3 per cent, and cessation of treatment promptly upon their appearance leads to recovery in the majority of all complicated cases. Complications are much less frequent in normal eyes than in eyes which showed abnormality at the outset. On the other hand primary optic atrophy itself does not constitute an absolute contra-indication to tryparsamide therapy, as shown by Woods and Moore.¹⁸³ Cady and Alvis¹⁸⁴ have stated that after a rest period of 30 days tryparsamide treatment may be resumed with little risk of further difficulty. Ophthalmologic control is highly desirable at the outset of all tryparsamide treatment, for the maximum risk of eye complications falls within the first eight injections. Ophthalmologic control should be directed, *not to the examination of the fundus of the eye*, but to exact perimetric tests of the visual fields and tests for visual acuity. Inasmuch as the subjective visual symptoms are even more important than objective changes, it follows that the befuddled or advanced parietic becomes a greater risk than the patient in whose observation entire confidence may be placed. This possibility must be borne in mind in the selection of patients for tryparsamide therapy.

The results obtained by tryparsamide therapy in neurosyphilis still lack satisfactory definition, largely due to the fact that remission is not identical with cure and that there is great variation in the definition of good or excellent results. Lorenz states, for example, that in neurosyphilis in general, of 317 patients observed after five to six years, 87 per cent remained permanently restored to physical health and mental efficiency. These results, however, seem to include all forms of neurosyphilis rather than general paresis alone. Lorenz's extended study and large material indicate that there is no definite clinical or serologic symptom-complex constantly associated with either good or poor prognosis, so far as results in tryparsamide and mercury treatment are concerned. An early favorable serologic response and active mental symptoms seem to have favorable prognostic significance.

Fever Therapy—Malarial Inoculation.—The literature on malarial therapy is enormous and constantly growing. Important summaries by

Gerstmann¹⁸⁵ and O'Leary and Brunsting¹⁸⁶ may be consulted. Although, as in the case of tryparsamide, the results of malarial treatment are still inaccurately defined, there seems at the moment little ground for question that the method is the most effective, best studied and most popular now available for the treatment of parietic neurosyphilis. Its advantages include the comparative shortness of the course, with results large in proportion to the time and money spent. The disadvantages include the marked discomfort of the treatment; the variations in convalescence, which is short and uneventful in some patients, prolonged and accompanied by serious complications in others; the occurrence of a definite mortality, steadily decreasing with larger experience and better selection of cases, to be sure, but none the less ranging still from 1 to 10 per cent; and the necessity for expert supervision and hospitalization, which interfere with the patient's occupation and earning power, if not already impaired.

As in the case of tryparsamide, fever-therapy results in paresis are striking, in tabes comparatively insignificant. This is particularly true of primary optic atrophy and gastric crises, in which it was hoped that more striking results might be achieved.

As compared with tryparsamide, malarial therapy seems to the author, on account of its definite mortality, to be a second choice. Perhaps the situation may be better defined by saying that the young, robust parietic with definite though early symptoms, who can afford hospitalization; who is likely to become uncontrollable under ambulatory conditions if the process is stirred up by any form of treatment; who must rapidly achieve a result before his own funds or those of his backers are exhausted; or who is approaching the age line spoken of below (45 years), is wisest to take the malarial therapy as a first choice. On the other hand, there does not seem at the moment, in view of the excellent tryparsamide results reported, and the steadily decreasing risk of eye complications under better technical management, any reason why asymptomatic neurosyphilis with a preparetic or "red flag" formula should be subjected forthwith to fever therapy. Six months' or a year's trial of tryparsamide, or even two years of tryparsamide, can frequently be carried by these patients without difficulty or embarrassment while they remain at work as effective members of the community. Where age, debility and nonsyphilitic complications are factors, tryparsamide also deserves first choice.

Malarial therapy need not and often should not be used to the exclusion of other methods in any given case. As the atmosphere of controversy on the relative merits of various forms of treatment subsides, combinations of fever therapy with tryparsamide and with standard treatment procedure will perhaps become the rule rather than the exception. The tonic course of neocarsphenamine now used by most malarial therapists, both to assist in the extinction of the malaria and to promote convalescence, can be succeeded immediately by the use of tryparsamide under proper control. The rules applicable to such cases do not differ from those in which tryparsamide is the initial choice.

The decision to employ fever therapy in a given case of neurosyphilis demands, if anything, an even more careful appraisal of the patient as a whole than that which is appropriate to the initiation of any form of treatment in late syphilis. In the writer's experience most of the unfortunate results of fever therapy have ensued upon an over-

enthusiastic frame of mind on the part of the therapist, upon the deliberate taking of a chance, and upon failure to identify fully and give proper weight to contra-indications. In the writer's experience, cardiovascular disease in any form is the most nearly absolute contra-indication to the use of malarial therapy or, in fact, to any form of fever therapy. With this complication in mind, the difficulty in appraising the cardiovascular reserve of a syphilitic patient over 45 years of age has led the writer to accept age 45 as the approximate upper limit for the unhesitating use of fever therapy. On the other hand, it is a matter for serious consideration whether patients under 40 years of age, who are in good condition, should be allowed to rely solely on tryparsamide effect, even though the results of this treatment have been good. In many if not in most cases, the younger patients should have the benefit of malaria.

Flare-ups of mental symptoms being part of the expected reaction to malarial therapy in patients showing the early signs of paresis, particularly of the excited or expansive type, proper provision must be made in advance for control and even commitment, if necessary, precisely as in the case of tryparsamide.

Cases are gradually accumulating which tend to indicate (see discussion of O'Leary and Brunsting's paper¹⁸⁶) that not all the effect secured by malarial inoculation is attributable to fever as such. Until this question is precisely evaluated, therefore, in the light of newer methods, Wagner von Jauregg's original point of view, based on experience with nonspecific methods, that an infection as well as fever is a necessary element in the therapy, continues to give malarial inoculation its superiority.

It is extremely difficult to evaluate the widely variant reports on the end-results of fever therapy. A rough statement which averages most of the reports indicates that one-third of the patients achieve excellent results with restoration to serologic and mental normality; one-third fall short of this goal but are none the less improved; and one-third fail of improvement, disappear from observation or die under treatment, whether from complications or the progress of the paresis as such. It must be recalled that in all probability the aggregate of patients subjected to malarial therapy in statistical evaluation is of a more unfavorable type than that subjected to other forms of treatment, and that this must show in the estimation of results and mortality.

Serologic improvement under malarial therapy is not often immediate. Weeks or even months, and possibly a year or two, may elapse before the serologic response becomes fully apparent. A number of observers, including O'Leary and Brunsting, have shown that this serologic response may take place even without continued antisymphilitic treatment. Ebaugh stated that existing evidence shows malaria to be a much more effective method of treatment in men than in women.

In view of the demonstrated effectiveness of malarial therapy, other methods of producing therapeutic fever must be regarded as still in the experimental stage, so far as the average case is concerned. Interesting and possibly important results may be expected from the chemical production in fever, as by the intramuscular injection of sulphur in oil. Nelson's very interesting recent modification of the technic of typhoid inoculation as a form of fever therapy, in which two small doses are administered—the first to initiate the febrile response and the second

at the height of the first fever crest to raise the temperature to a high level, also has very interesting possibilities. Diathermy, if clinically of equal effectiveness, may supersede inoculation and foreign protein techniques if the risk of burns can be completely controlled. There can be no question that a procedure such as malarial therapy, which involves the inoculation of a patient with one disease to cure him of another, has an intrinsically repugnant quality that, despite its effectiveness, still gives it somewhat the flavor of a makeshift.

Management of General Paresis.—A few practical considerations apart from the previously discussed syphilotherapeutic techniques are of interest in dealing with the potential or actual parietic patient. An early conference with relatives is highly desirable and a responsible person should be kept informed step by step of the intended and actual treatment and the possibilities of complications. The patient's business affairs should at the earliest possible moment be gotten into safe hands and persuasion will sometimes secure a power of attorney where commitment might otherwise seem to be unavoidable. In general, commitment leaves a certain amount of psychic scar in a recovered patient and injures his social and business status materially so that it should not be thoughtlessly or rashly carried out. Sequestration in a private hospital or sanitarium is often possible without actual legal formalities and records. Remission should be mentioned to the relatives as a possibility and they should also be warned of the probability of a flare-up of symptoms in the more excited type of case, when treatment is first instituted. If excitement is very definite on first examination, hospitalization is practically unavoidable. If the patient is depressed, suicide constitutes a serious risk. Little should be said about prognosis and this should be especially guarded if convulsive, hemiplegic or aphasic accidents have been noted. The family must be warned about the risk of violent outbreaks; the excessive and indiscriminate sexual activities of the excited parietic must be controlled even to the point of sequestration. The writer's personal observation is in favor of a preliminary course of standard treatment with **arsphenamine, mercuric succinimide and iodide or arsphenamine and bismuth** before other therapeutic measures are adopted—this, of course, provided the patient is in reasonably good condition mentally. On the other hand, many therapists would feel this a waste of time. The writer believes, however, that it reduces the severity of therapeutic shock manifestations. The old or senile parietic is often almost better let alone than subjected to the hammering of modern treatment. The estimation of prognosis in paresis is exceedingly difficult and this is particularly true where signs of deterioration have occurred. The deteriorated parietic can be roused from his comparative lethargy to become one of the most obnoxious, difficult, troublesome and even dangerous elements in a family or community life, by the use of either tryparsamide or fever therapy.

Management of the Tabetic.—Just as general paresis is the field *par excellence* for modern tryparsamide and fever therapy, so tabes, in spite of recent therapeutic innovations, remains the field *par excellence* for medical and neurologic judgment in treatment individualization, and for the use of the standard and even some of the older methods of syphilotherapy. The patient showing the earliest initial signs of tabes, provided the process be not too acute or rapidly progressive, will, however, stand systematization well and, in fact, may do better under it

than under too much therapeutic coddling. A preparatory treatment with mercuric succinimide intramuscularly and large doses of iodide by mouth or intravenously is an excellent beginning if the patient can make the necessary frequent visits to the office. Bismuth also constitutes an excellent preparation and six to ten injections may be employed before an arsphenamine is considered. The preference for the therapeutic effectiveness of "606" extends to the treatment of tabetic neurosyphilis in its earlier stages, but a combination of neoarsphenamine and bismuth is reasonably satisfactory in many cases. Courses of eight to twelve injections may alternate with rest periods of one to three months, the rest periods being determined in the early case by the serologic and in the late case by the symptomatic response. Early tabes stands therapeutic hammering very well and if the eyes are entirely normal, a resistant serologic picture may be dealt with by the use of tryparsamide. A total of 20 to 30 neoarsphenamine injections is an average requirement, the treatment being tapered off with bismuth and iodide if the serologic response has been satisfactory. Inunctions are still usable but their tendency to exaggerate symptoms associated with focal infections makes them less satisfactory, on the whole, than bismuth, if the patient can be kept under medical control.

It is essential to emphasize the fact that, in common with all other aspects of late syphilis, the neurosyphilitic and particularly the tabetic patient cannot be discharged completely from observation throughout life. The principal reason for this is the undoubted occurrence of symptomatic unfavorable progress in the presence of completely negative serology, both in the blood and the spinal fluid. Accordingly, every tabetic should be subjected to periodic neurologic survey as well as to serologic test. Particularly careful account should be taken of the behavior of the bladder and sexual mechanism, any increased frequency of pain and any new developments in the way of paresthesia. Vision should be periodically rechecked by an ophthalmologist, using perimetric field and acuity tests, in order to detect any suggestion of the onset of primary optic atrophy.

Three groups of nonspecific therapeutic measures deserve special emphasis in dealing with the tabetic. The first of these is **attention to focal infections**. The comfort of a tabetic patient can be completely destroyed through repeated sieges of lightning pains which clear up at once upon the removal of dental foci, for example, which are scarcely detectable by the x-ray. I have repeatedly seen the chase for a focus of infection, with successive periods of temporary relief following each new discovery and removal, run the gamut of an x-ray negative and dentally approved molar; a foreign body in the upper jaw; a chronically infected prostate; a fistula in ano; and an atonic infected colon. The second nonspecific measure essential to the rehabilitation of the tabetic is attention to the bladder and renal function. As early as possible after a tabetic comes under medical care, his blood urea and phenolphthalein functional tests should be performed and an effort made to estimate the degree of urinary retention and the possibility of bladder infection. This may involve catheterization, which should be undertaken under only the most rigid precautions against infection, and should never be undertaken except by an expert urologist if the patient has been leaking and dribbling for some time and undergone thereby renal functional impairment. Patients may be precipitated into uremia,

precisely as in retention due to prostatic hypertrophy, by an injudicious first catheterization. Depending upon the degree of atonic change (cord bladder), proper measures, including repeated catheterization and irrigation if infection is present, must be carried out. It is remarkable, however, to what degree a seemingly atonic tabetic bladder will recover function under thorough-going antisyphilitic and urologic treatment. The patient should be warned against taking up a catheter life and should be trained as far as possible in the emptying of his own bladder without instrumentation through posture, applications of heat, and so forth. The urine can frequently be passed completely at least once in 24 hours in conjunction with the bowel movement, or while sitting in a warm bath. It is not too much to say that every advanced tabetic is a potential uremic.

The control of pains and paresthesias, while quite largely dependent upon treatment and often responsive to relatively mild measures such as a single course of bismuth or bismuth arsphenamine sulphonate, is in the long run a rather difficult matter. It is in this connection, as well as in the raising of the general level of well-being of the tabetic, that rest, change to a warm winter climate, avoidance of strenuous over-exertion and the occasional judicious use of mild sedatives and analgesics become an art. Occasional courses of colon irrigation, careful instruction in anticonstipation régime, irradiation with ultraviolet light and sheer encouraging talk, all play their parts from widely varying angles. The physician in charge of such a patient should not too readily resort to antisyphilitic measures but should first carefully canvass the field of possible causes and nonspecific methods of relief. When antisyphilitic measures are resorted to in the late tabetic, a tonic procedure as distinguished from a treatment for arrest is often indicated. The essentials of tonic therapy include small doses of neoarsphenamine (0.45 Gm.) once a week for six to ten weeks. **Bismuth arsphenamine sulphonate**, 0.1 Gm. (1.5 Gr.) intramuscularly every fourth day, for ten or fifteen injections, may initiate a marked upward trend. Several such courses at intervals of three or four months may be sufficient to place a tabetic "wreck" on his feet and maintain him in reasonable comfort for a long period.

The casual use of morphine for the relief of any of the painful symptoms of tabes, including crises, cannot be too vigorously condemned. The combination of tabes and morphinism is a therapeutically impossible one and inevitably leads to deterioration. The impulse to give a hypodermic for the relief of pain should be drilled out of instead of into medical students. Morphine is only rarely a necessity in dealing with the painful complications of neurosyphilis if the above mentioned methods of procedure be given their proper place.

Tabetic Crises.—The tabetic crisis, most often of course gastric, is the most obstinate and discouraging of all complications. Beginning in the periodic recurring attack of pain, with or without vomiting, or of vomiting, with or without pain, the gradually increasing frequency of the seizures ultimately wrecks the patient's morale and brings about a fatal termination through exhaustion and intercurrent disease. Under standard intensive treatment to which, unfortunately, neither tryparsamide nor malarial therapy has made any notable contributions, 24 per cent of these patients sustain an amelioration of symptoms with reduction in severity and length of attacks sufficient to permit them to get

about. The combating of the neurosis, the fear and hopelessness which seems to be a psychic accompaniment of the condition, is often as difficult as any phase of the treatment. The intrarectal use of **chloral and sodium bromide**, 40 Gr. (2.66 Gm.) each in an ounce of water, has been shown by McFarland¹⁸⁷ to give very marked relief if the patient is kept in a darkened room with the buttocks elevated. No habituation seems to develop. Magnesium sulphate intramuscularly is not particularly helpful. Occasionally remarkable success in aborting a gastric crisis may be secured through the intramuscular injection of 1 to 2 cc. of a 1:1000 solution of **adrenalin**. The victims of gastric crises must be encouraged to eat heavily between attacks, a thing which they are not inclined to do because of their fear that the trouble is actually with the stomach rather than in the nervous system. All the collateral factors involved in dealing with advanced tabes should have attention in dealing with gastric crises.

Ataxia.—Tabetic ataxia makes a relatively poor response to treatment for neurosyphilis as such, in the advanced case, though the acute early ataxia occasionally observed responds very well. The tabetic ataxic patient can be taught to substitute his eyesight for his sense of motion and position and to practice muscle reëducation and balance by drill in placing his feet and keeping them "in the corner of his eye" as he walks. The psychic factor in ataxia is quite apparent in any considerable experience and reassurance plays no small part in recovery of control.

Primary Optic Atrophy.—The only genuine ray of hope in the treatment of primary optic atrophy within recent years has been provided by Moore's¹⁸⁸ work on the effects of intraspinal therapy. Moore has apparently brought out quite clearly that the outlook is dependent on the degree of visual impairment and that the earlier the patient can be placed under treatment, the better the prospects for arrest. Unfortunately, primary optic atrophy is relatively uncommon and few observers have had the opportunity of studying or treating more than a very limited number of cases. When thus viewed from the isolated-case standpoint, it must be said that practically all favorable or quasi-favorable results can be matched with failure or rapid decline in vision or even an actual disaster, following the use of identical methods of treatment. It is therefore small wonder that ophthalmologists are profoundly pessimistic about the virtue of any form of antisiphilitic treatment. Arsphenamine is apparently in disfavor among ophthalmologists; but Moore's most recent series shows, apparently convincingly, that while spectacular results certainly cannot be expected, the intraspinal therapy (Swift-Ellis) of early cases does lead to more arrests and even to some visual gain in contrast with untreated or ineffectively treated cases.

FAMILIAL AND PRENATAL SYPHILIS

Prenatal syphilis, by which term is meant syphilis acquired *in utero* and often mistakenly called congenital syphilis, is an extensive and important field of modern syphilology and one in which it would appear, from progress in recent years, extraordinary results can be obtained by preventive effort. The following brief statement of principles, while rather dogmatic, points the way satisfactorily to an attack upon the familial aspects of the problem.

Every syphilitic child may be accepted as *prima facie* evidence of

the existence of a syphilitic mother. Third-generation syphilis, while reported, has not yet, in the writer's opinion, withstood critical review and must at best be an excessive rarity if it exists at all. Paternal transmission of the disease to the fetus born of an uninfected mother is likewise an entity which even the French, who have championed it for many years, have apparently generally accepted as nonexistent. There are, of course, cases in which the explanation of paternal transmission would be most acceptable could it be verified, but these must be regarded as still within the "penumbra of doubt." Most syphilitic mothers have syphilitic husbands. Repeated surveys of familial syphilis have shown that the father is the overwhelming source of the mother's infection and that this infection takes place as a rule within the first three years of married life. Strandberg's¹⁸⁹ study of 250 marriages in which syphilis was present in one partner or the other showed that only 27.6 per cent escaped all consequences in their married lives. The disease was transmitted to the partner later than the fifth year in 20 per cent of his cases. Inasmuch as there are many reasons for believing that the portal of entry in sexual relations may be the cervix (see, for example, Davies¹⁹⁰) and that the infecting medium may be the semen, it is apparent that the control of infectiousness in marriage cannot be left merely to any such consideration as freedom from visible lesions.

The moment, therefore, that the physician encounters syphilis in any person it is a part of his professional obligation to follow the trail up or down toward parent or child, as the case may be. The detection of prenatal syphilis depends not alone on serologic tests but upon the stigmas or physical characteristics induced by the disease when acquired *in utero*; and for this reason, while a round of Wassermann tests on a family is of material assistance, it cannot take the place of a personal inspection of all the members, if this is possible. Much follow-up effort is profitably devoted by clinics for syphilis to the bringing in of the entire family in which the disease has once appeared.

If examination of the family is the first step, the detection of syphilis in the pregnant woman is the second and often the more practical step in following the trail of the disease. The popularization of a single measure, now easily within the reach of the large majority of physicians, would go as far in a preventive way in dealing with prenatal syphilis as has the Credé instillation of silver nitrate in the prevention of gonorrheal ophthalmia. As part of the routine prenatal care of every woman a blood Wassermann or precipitation test for syphilis should be had by the third month and this should be repeated by the seventh month of every pregnancy. In this way the syphilis acquired in the course of marriage and the syphilis all too frequently acquired as the result of the extramarital infection of husbands during their wives' pregnancies could be detected. There is, of course, a margin of error in this generalization, for serologically negative mothers may, none the less, carry syphilitic infection and sero-positive mothers may give birth to healthy children. The detection of syphilis in the mother is, however, the most rational approach to the prevention of syphilis in the prenatally infected child.

Identification of syphilis in the newborn child should be made by careful physical examination of the child at birth for the suspicion-arousers presently to be described; by examination of the placenta in the gross in connection with delayed delivery of the placenta; and by the serologic test on the cord blood. The effort to detect prenatal

syphilis should not, however, by any means end here. Infants with unquestionable syphilitic infections may be sero-negative for days and even for weeks after birth and may not before the second month show the disease which they acquired *in utero*. Wherever, therefore, there is any ground for suspicion of a child's antecedents, repetition of the serologic tests after the sixth or eighth week is a reasonable measure of precaution, and a test after the tenth day has materially greater value than the cord Wassermann alone.

Knowledge of the earmarks of prenatal syphilis in the infant and in the adolescent, as well as the peculiarities of syphilis in the gravid and childbearing woman, is essential to the detection of the maximum amount of prenatal syphilis in medical practice. The peculiarities of syphilis in the mother, the suspicion-arousing symptoms and signs in the infant, and the stigmas of tardive prenatal syphilis must therefore be reviewed.

Suspicion-Arousing Elements and Peculiarities of Syphilis in the Woman.—Syphilis in women, generally speaking, runs a milder course than in men and, as has already been stated, tends more to constitutional than to visible and therefore easily recognizable manifestations. This is particularly true of its infectious years. An additional difficulty is introduced into the diagnosis of syphilis in the woman by the inhibitive effect which pregnancy, generally speaking, exercises upon the course of the disease. So marked is this effect that it is almost permissible to regard repeated pregnancies as a form of treatment for syphilis and their high protective value is evidenced by the frequency with which one meets the mothers of considerable families of syphilitic children who themselves are practically devoid either of clinical or of serologic evidences of the disease. Emphasis is, of course, always laid upon the importance of the history of miscarriage, and this does indeed constitute an important suspicion-arousing element. The theoretical course of a succession of syphilitic pregnancies tends from abortion through successively longer and longer pregnancies to the birth of stillborn or macerated, then premature living syphilitic, and finally of full-term living syphilitic or apparently healthy offspring. In practice this sequence is seldom realized. The characteristics of syphilitic miscarriage in general are: a tendency to the birth of premature fetuses, macerated or intact, rather than early embryos; then to an alternation of miscarriages with stillborn or living syphilitic children. In the writer's own experience, 45 per cent of 117 cases produced the living syphilitic child as the product of the first pregnancy. Estimates of the frequency with which a stillbirth with macerated fetus indicates syphilis in the mother and child range from 40 to 80 per cent. Non-syphilitic miscarriages are characterized more by a tendency to terminate time after time at about the same period of gestation, usually the third or fourth month. The longer the series of miscarriages, the less likely it is to be syphilitic. The nonspecific beneficial effect of a course of arsphenamine in these cases cannot be accepted as proving a diagnosis of syphilis in the mother. In the later years of the disease the gradual, almost physiologic, decline of infectiousness, together with the inhibitive effect of repeated pregnancies, may make it absolutely impossible to identify the mother's syphilis short of a long period of observation. In fact, it is these suppressed cases which have given so strong a currency to the conception of paternal transmission. It must not be forgotten that syphilis in the mother may be suspected through

examination of the father, even though the mother herself is practically free from signs. In carrying through this examination, if the father shows evidence of neurosyphilis, the mother's spinal fluid should likewise be examined, even though she be asymptomatic, for conjugal neurosyphilis is too common to be allowed to escape through incomplete examination, and neurosyphilis in the woman, like other manifestations of the disease, runs a milder and more occult course which makes direct recognition a more uncertain matter.

Suspicion-Arousing Symptoms and Signs in the Child.—These begin with inspection of the placenta. A typically syphilitic organ is larger than normal, the relation to the weight of the fetus being as 1 to 4, as compared with 1 to 6 for the normal. It is softer, paler, almost friable, with yellowish patches and an occasional fatty sheen. The endarteritis, as seen under the microscope, is stressed by Williams,¹⁹¹ but placental characteristics are not universally accepted as having great weight. The proportion of negative blood Wassermann reactions on syphilitic infants at birth may be as high as 37 per cent (Jeans¹⁹²) but by the end of the first few weeks, as already stated, the test almost invariably gives a strong positive. The syphilitic infant, contrary to common conception, is usually at birth reasonably well nourished and of good appearance. The chief symptoms may be summarized as follows: the eruption is rare before the third week and shows a distinctive tendency to appear about the face, mouth, the anogenital region, and the palms and soles. It may be macular, maculopapular, secondarily eczematous, and is often infected. Condylomas and mucous lesions are usually abundant and the bullae on which so much emphasis is laid are present on the palms and soles in only 10 per cent of cases. Snuffles is a valuable early suspicion-arouser as common as the eruption. If it is hemorrhagic it is almost diagnostic. The cry is very suggestive; a peculiar cracked, aphonic, wheezy effort, strikingly different from the clear-cut tones even of a feeble though otherwise normal child. Hacking of the lips with the formation of fissures across the vermillion border, especially of the upper lip and the middle portion of the lower, and infiltrative fissures with radial arrangement at the angles of the mouth and on the cheeks and chin with eczematous changes, appear in more or less advanced cases. They are, however, not so common as the hacking. Splenic enlargement is rated as almost diagnostic before the fourth month. A very characteristic picture is that of the so-called Parrot's pseudoparalysis: a flaccid limpness or hanging of the upper extremities or more often a spastic condition of the lower extremities, presumably due to painful movement, and attributable to osteochondritis and epiphysitis. The osteochondritis and epiphysitis with osteomyelitic changes may be recognized by palpable enlargement and tenderness of the ends of the long bones, oftenest of the upper extremities. Fusiform involvement of the shaft is also recognizable on palpation. Epitrochlear adenopathy is stressed by some writers, and saddle deformity of the nose may sometimes be very pronounced. The pulmonary, hepatic and marasmic symptoms, melena, icterus, and meningitis are comparatively rare but should, of course, always arouse suspicion. As differential elements in the eruptive manifestations, emphasis should be placed upon the papular form of the ordinary diaper erythema, which sometimes apes an anal syphilid almost perfectly, and the extensive pustular and eczematoid patchy eruption known as impetigo neonatorum or Ritter's disease.

Diagnosis of Tardive Prenatal Syphilis.—Prenatally acquired syphilis appearing in early infancy shows a curious mixture of the late and early characteristics of the postnatally acquired form of the disease. Prenatal syphilis in which the early manifestations are suppressed, inconspicuous, or soon overcome by the resistance of the patient, passes over into the so-called tardive form. It is a reasonable presumption that tardive infections probably represent earlier uterine inoculation so that the disease has had the opportunity to modify the structural development of the child and, similarly, to be modified and reduced in virulence by the defense mechanism of the mother and the fetus. Thus it comes about that tardive prenatal syphilis is essentially a combination of late syphilis with developmental changes, some of which suggest an influence upon the endocrine mechanism and the growth centers. From the activities of the disease considered as forms of late syphilis arise the most active and, in some cases, life-endangering manifestations; from the developmental changes come the stigmas or pathognomonic, presumptive and debatable signs of the disease upon which diagnosis, and particularly the suspicion which leads to diagnosis, usually rests. For purposes of condensation the symptoms and signs of tardive prenatal syphilis may be grouped in order of frequency under the groups of structures most commonly involved. This arrangement is carried out in Table V.*

TABLE V.—GROUPED SYMPTOMATOLOGY OF TARDIVE PRENATAL SYPHILIS¹⁹³

<i>Eye</i>	<i>Stokes Series</i>	<i>Osborne Series</i>
Interstitial keratitis	52 per cent	20 per cent
Choroiditis	8 "	
Iritis	7 "	
Strabismus	4 "	
Ptosis	3 "	
Optic atrophy	2 "	
Dacryocystitis		
Retinitis pigmentosa		
Hyalitis		
Vitreous opacities		
Uveitis		
Night blindness		
<i>Skeletal Lesions</i>		
Frontal bosses	44 per cent	10 per cent
Saber shins	43 "	7 "
Facies	21 "	10 "
Scaphoid scapula	20 "	5 "
Epiphyses, enlarged	13 "	
"Arthritis"	9 "	
Clavicles, thick	4 "	
Hydrarthrosis	3 "	3 "
Dactylitis	2 "	
<i>Ear, Nose and Throat</i>		
Characteristic teeth	32 " (2d dentition)	18 "
Saddle nose	30 "	4 "
Other nose lesions	19 "	
High palatine arch	19 "	8 "
Deafness	10 "	4 "
Rhagades	6.5 "	
Gumma, nose and throat	6.5 "	
Nasal obstruction	5 "	
Cervical glands	2.5 "	
Perforated palate	1 "	

* This series illustrates the influence of age on symptomatology. The WaR was positive in 95 per cent of Osborne and Putnam's patients, and symptoms and signs proportionately lower, inasmuch as the ages of their patients were under ten years in 75 per cent, while 65 per cent of the writer's were over nine years.

<i>Nervous and Mental</i>	<i>Stokes Series</i>	<i>Osborne Series</i>
Neurosyphilis	26 per cent	6 per cent
Mentally retarded	25 "	6 "
Nervousness	22 "	
Precocity	12 "	
Convulsions	2.4 "	
Paralyses	2.0 "	
<i>Visceral</i>		
Liver, enlarged	19 "	
Spleen, enlarged	14 "	
Nephritis	1 "	

From this table it will be apparent that the eye leads all other structures in providing chief complaints and symptomatic clues upon which to develop a diagnosis of tardive prenatal syphilis. It is followed by skeletal lesions, ear, nose and throat lesions, nervous and mental symptoms, and visceral symptoms in the order named.

Blood Serologic Tests.—In infancy the blood serologic tests have practically an efficiency of 100 per cent after the eighth week of life. This peak of efficiency gradually declines, as in the case of acquired syphilis, and in the writer's experience its efficiency approximates 90 per cent in the first decade of life, 65 per cent in the second, 46 per cent in the third, and 15 per cent in the fourth decade (over 30 years). It is, however, a notable fact that the onset of an active complication such as interstitial keratitis, even in the later years, will be accompanied by the appearance of a positive Wassermann in a case previously negative over a long period. After 20 years of age, more than half the cases are identified by clinical signs.

Diagnosis of Tardive Prenatal Syphilis by Developmental Stigmas and Signs.—There are only two or possibly three pathognomonic signs of tardive prenatal syphilis. The first of these is interstitial keratitis, already described; the second is Hutchinsonian upper central incisor teeth; and third perhaps the Moon molar. Even the almost pathognomonic saber tibia can be simulated to a disconcerting degree by anterior bowing in rare cases of rickets and by the so-called nonsuppurative osteitis of the tibia. It is therefore probably wiser to classify the landmarks as major, secondary, minor and debatable. *The major landmarks* include (1) the positive blood Wassermann reaction; (2) interstitial keratitis; (3) Hutchinsonian incisors; (4) Moon or mulberry molars; (5) eighth nerve deafness; (6) saber tibiae due to osteitis and periostitis and simple hypertrophy due to abnormality of the growth centers; (7) osteitis of the nasal septum with snuffles and saddle bridge; (8) epiphysitis and osteochondritis; (9) early splenomegaly; (10) typical rhagades and sears; (11) early dactylitis; and last, but by no means least, (12) the facies of prenatal syphilis. *The secondary landmarks* differ from the major in that they do not suffice for a diagnosis, alone or in combination among themselves, as do the major landmarks. Secondary characteristics include: (1) frontal bosses; (2) aplasia of the incisor teeth; (3) scaphoid scapula; (4) marked disturbance of the age development ratio; (5) precocity and high nervous irritability; (6) early epitrochlear adenopathy; and (7) the high, narrow palatine arch. *Minor stigmas* include venous ectasia, marked general hypertrichosis, ulnar deviation of the middle fingers, constitutional subnormality, backwardness, hypertrophic frontal suture, craniotabes and bilateral dacryocystitis in childhood. Among the *debatable or unevaluated signs* that

have been proposed should be enumerated Carabelli tubercles or accessory cusps on the molar teeth, retromastoid adenitis, persistent infantile hydrocele, hypertrophic thymus and thymic abscess, alopecia areata in childhood, and knock-knee elbow.

By way of general commentary on these signs, the Hutchinsonian upper central incisor deserves special mention. The diagnosis can be made only by the second-dentition teeth, but it is possible to demonstrate their presence in the jaw before eruption, as shown by Stokes and Gardner,¹⁹⁴ and more recently by Meyer-Buley.¹⁹⁵ The typical Hutchinsonian tooth shows a definite hypertrophy of the lateral denticles and a corresponding suppression of the middle denticle. This gives the tooth either a screw-driver shape with marked anteroposterior thickening, or a lateral bulge with a central notch. The notch, however, is not absolutely necessary in diagnosis, and Hutchinsonian teeth can be recognized without it. The so-called "mulberry molar," rated by many observers as quite as characteristic of prenatal syphilis as the Hutchinsonian incisor, is a modification of the basic structure of the sixth-year molar by which the cusps are reduced to extremely small remnants which usually rapidly decay while the enamel ridge is markedly hypertrophied. This combination of changes, if caries has developed, produces the so-called "honeycomb molar" in which the small abortive decayed cusps are replaced by pits in the grinding surface of the tooth. Other anomalies of dentition are frequent in prenatal syphilis but of no conclusive diagnostic value. The pegging of the incisors may be suggestive but is not to be overrated. Nonspecific serrations and enamel defects cannot be regarded as distinctive of prenatal syphilis.

A corneal nebula and new-formed vessels, interstitial keratitis, and the active keratitis itself, when identified by the ophthalmologist, may be accepted by the clinician as a pathognomonic sign of prenatal syphilis. It is known to occur very rarely in secondary syphilis in association with chancre of the eyelid, but this combination must be excessively rare. The more frequent diagnostic confusion possibilities arise from the residua of tuberculous keratitis which must of course be differentiated by an expert.

The saber tibia in well marked cases is, of course, easily recognized. Emphasis should be placed upon the fact that the change is one of hypertrophy of the middle third and that a mere serration or roughening of the anterior edge of the tibia, or even a very slight bow with a sharp edge, does not necessarily justify a diagnosis. The x-ray is often of material assistance in demonstrating old osteitis, which is more often responsible for the change than is periostitis. Tender points characteristic of syphilitic periostitis should, however, be searched for. The so-called Hutchinsonian triad of deafness, interstitial keratitis, and Hutchinsonian incisors is rarely seen in its entirety.

The facies of prenatal syphilis constitutes to the expert one of the most interesting and helpful aids in diagnosis. It is not wise, however, to attempt to use this criterion in diagnosis without a considerable experience drawn from life rather than merely from textbook description.

Neurosyphilis and nervous disorders are an important group in the symptomatology of tardive prenatal syphilis. The proportion of spinal fluid abnormality recognized by systematic examination ranges from 20 to 40 per cent and is largely dependent upon the time at which the examination is performed, the higher proportion occurring in syphilitic

infants (Jeans). The onset of juvenile general paralysis may be veiled by the youth of the patient and lacks the striking features of the adult type, in part because of the undeveloped nature of its victims. Epileptiform seizures, mild grades of conduct disorder, and imbecility are the presenting symptomatic aspects in most cases. Not infrequently before onset, the child may present a normal or even a precocious mentality. Failure to pass a grade in school may be the first warning; and months, and even years, of slowly progressive retardation may only finally be unraveled as the dementia becomes complete, by an examination of the spinal fluid showing the characteristic findings. Juvenile tabes runs a milder course than the acquired type, and signs may be the chief aids to diagnosis with a comparative insignificance of symptoms. Cerebral arteritis, epilepsy, and spastic diplegia are, of course, known to occur in prenatally syphilitic children and the proportion of outright mental deficiency which is identified as syphilitic by the positive Wassermann reaction in childhood is about 6 per cent.¹⁵⁶ More important, from the therapeutic standpoint, is the prenatally syphilitic "bad boy." Extraordinary responses, and the actual reform of almost criminal tendencies may be noted under thorough-going treatment of the unmanageable prenatal syphilitic child.

Sero-positive, clinically negative, tardive prenatal syphilis exists and furnishes some of the puzzles of syphilologic practice. It is a great mistake to suppose that prenatally syphilitic individuals are necessarily marred, scotched, and more or less seriously damaged by their infection. There is a considerable proportion who present not only every evidence of good health, but actual physical beauty and mental superiority. Among these patients the unaccountable presence of a repeated, strongly positive blood serologic test comes to the examiner as a great shock. A thorough-going search for the stigmas of the disease not infrequently helps out by the identification of a pair of Moon molars or a combination of minor stigmas. Such patients may go through life without a significant complication and their positive blood serology may present extraordinary resistance even to intensive treatment procedures. All such patients as well as patients presenting actual stigmas of prenatal syphilitic infection should be given the benefit of the thorough-going routine and complete examination for all forms of syphilitic involvement, including an examination of the spinal fluid, if their age is less than 25 years.

Prevention of Prenatal Syphilis.—Prenatal syphilis offers one of the richest opportunities for preventive effort in the entire field of syphilology. The possibilities arrange themselves under four heads.

1. *Control of the transmission of syphilis* in sexual intercourse and conception.

2. *Limitation of conception* to periods when infectiousness is either nonexistent or controlled.

3. *Preconceptional treatment* of one or both partners.

4. *Treatment of the pregnant woman* and through her of the unborn child.

The control of prenatal syphilis rests essentially, in the large majority of cases, upon prevention of the infection of the mother. Such prevention goes back to first principles in time-treatment relations. The fact that it is the arsphenamine rather than the heavy metal phase of treatment which controls infectiousness makes it essential that this drug be used whenever the possibility of transmission arises in marriage or sexual

relations. If the infected partner or partners have been carried through the described standards for the treatment of early syphilis, infectiousness may be considered as having been as nearly controlled as possible. The fact that serologic tests alone cannot serve as proof that either partner to a sexual relation is noninfectious must also be constantly borne in mind. The general time rule that infectiousness in syphilis diminishes toward the vanishing point in the course of the first five years has general though unfortunately not absolute applicability to the transmission problems involved in sexual intercourse and marriage. Every effort should be made by the physician in charge of an infected patient to postpone unprotected sexual intercourse and conception until after five years have elapsed from the date of the infection. Where this date cannot be established with any certainty, additional emphasis on treatment factors is advisable.

Empirical rules based upon the duration of the infection, upon serologic tests, and upon treatment itself, are thus all seen to have a definite and often a liberal margin of error. When the attempt is made to guide the situation through the coöperation of a half-comprehending patient who is obliged to conform blindly to irksome and, in his opinion, frequently unnecessary restrictions, it will be apparent that the worth of conception- and infection-controlling methods is at best limited. The writer has felt it necessary to advocate more and more the absolute control of conception by mechanical means which coincidentally prevent the entrance of possibly infected semen into the woman's genital tract. If the infected individual can be induced to postpone marriage or sexual relations until the completion of the optimum infection-preventing course of arsphenamine and heavy metal treatment, and can be induced throughout the first five years of the disease to adopt protected intercourse and conception control at such times as he is not directly under the influence of the sterilizing effect of arsphenamine, more will probably be accomplished than by any series of time rules ever devised.

An element of inevitable uncertainty enters into the control of transmission of syphilis from mother to child. This is the difficulty of absolutely establishing noninfectiousness in the mother throughout any period corresponding to that of gestation. If the cure of the future mother by treatment were absolutely demonstrable, the situation, of course, would be greatly simplified. As the matter now stands, without absolute proof of cure, the best protection of the child at the present time will consist of treatment of the mother in anticipation of, as well as during, pregnancy. It appears, from the observations of Cooke and Jeans,¹⁹⁷ that pregnancies after the first are not protected unless treatment is continued during them. The question as to whether or not the father shall receive preconceptional treatment for a syphilitic infection depends very largely upon the status of the individual case but in general the writer is inclined to feel that **preconceptional treatment of both parents is the wisest rule**. That such treatment does not reduce the likelihood of conception is evident from the way in which arsphenamine courses in a syphilitic patient have a trick of terminating in a pregnancy. The amount and kind of treatment administered as preconceptional preparation must vary with the individual case but in general should include both **arsphenamine and a heavy metal**. The spirillicidal activity of **bismuth**, however, has increased the latitude

of choice in this matter, and bismuth alone may be sufficient in certain cases.

Treatment of the Pregnant Woman.—This, by far the most important because of its practical bearing on all the available methods for dealing with the transmission of syphilis to the child, is one of the notable advances of the last ten years. To bring home its tremendous importance for the welfare of the syphilitic mother and her unborn child, the writer quotes only one, and that the most complete and important series of figures from the many now extant. Boas and Gammeltoft¹³⁸ in a total of 201 cases of syphilitic mothers receiving no treatment for the disease found that 96.5 per cent of the children were syphilitic and 3.5 per cent healthy. Of 87 syphilitic mothers receiving mercury before pregnancy but none during it, 90 per cent of children were syphilitic and 10 per cent healthy. Of 15 mothers receiving an arsphenamine before pregnancy but none during it, 80 per cent of children were syphilitic and 20 per cent healthy. Of 111 mothers receiving mercury only during pregnancy, 72 per cent of children were syphilitic and 28 per cent normal. Of 26 mothers receiving arsphenamine before and mercury during pregnancy, 27 per cent of children were syphilitic and 73 per cent normal; while of 105 mothers receiving arsphenamine during, or both before and during pregnancy, only from 15 to 20 per cent of children were syphilitic, and from 80 to 85 per cent normal. It will be seen without further comment that the recognition of syphilis in the pregnant woman and the administration of **combined arsphenamine and heavy metal** treatment controls the transmission of prenatal syphilis to an extent that should make possible enormous reductions in the incidence of the disease. The principal question raised in connection with antisyphilitic treatment of the pregnant woman has been that of the mother's tolerance under the added load entailed by the pregnancy. This has led to very conservative practice in dosage and amount of treatment administered. A number of the published reports describe treatment measures far below even a reasonable standard for the acquired forms of the disease. With the advent of bismuth especially as a substitute for the nephrotoxic mercury, there is no reason why these measures should not be markedly intensified. Bismuth arsphenamine sulphate has not as yet received a satisfactory trial in the treatment of the pregnant woman; but **neoarsphenamine and bismuth**, simultaneously or in alternation, are certainly very well tolerated, and if the dosage of the neoarsphenamine does not exceed 0.45 Gm. and the interval between injections is not reduced below five days, the pregnant woman can easily receive if necessary in the earlier or middle months of her pregnancy an amount of treatment corresponding quite closely to that described for the therapy of early syphilis. Antisyphilitic drugs do not have any notable degree of abortifacient effect when employed as described. The principles with reference to the avoidance of rest intervals may perhaps be somewhat relaxed in dealing with the treatment of the pregnant woman, but no positive information on this matter is available. In general, while a pregnancy exercises an inhibitive effect, there are examples to the contrary, and the abrupt cessation of treatment a month or six weeks before the close of a pregnancy provides just the length of time necessary for a relapse which will involve the child just before or at birth.

In the case of the mother with latent syphilis of one to five years'

duration whose blood Wassermann reaction is positive, treatment should be begun as soon as the pregnancy is recognized and continued at least with bismuth after 12 to 20 neoarsphenamine injections until term. The question of treatment in older multiparae must be to some extent individually decided and be correlated with the amount of treatment that the patient has previously received and the general course of the infection.

These plans cannot be arbitrarily applied to any case or regarded as infallibly effective, but they follow the general outline recently established in the treatment of syphilis. The pregnant woman should not be overloaded, but her tolerance is usually greater than is expected. Signs of reactivity must, however, be taken more seriously than in the normal case. The urine, blood pressure, and skin must be closely watched. Spinal fluid examination should in general be omitted until postpartum. **Neurosyphilis**, if present, as judged by clinical signs, **is best treated by routine measures**; and inasmuch as there is no evidence as to the effect of tryparsamide upon the optic tract of the fetus, this form of therapy as well as malarial treatment should be excluded. There is usually ample time for such measures after the pregnancy terminates.

Postpartum Observation.—Adequate postpartum observation is a paramount obligation. None of the results as yet published can, in point of time alone, answer the question as to whether the seemingly well child is actually well. The critical years, seventh and fourteenth, second dentition and puberty, must be safely passed in a considerable group of cases before treatment of the mother can be evaluated for the child. Under the conditions of public clinics, a year or two of observation is all that most observers feel can be expected for the rank and file, but every effort should be made to extend this by those who have opportunity. Nothing more than encouragement and evidence of symptomatic rather than curative effect can be drawn from the usual maternity service reports which embrace the condition of the child ten days to two months after birth. Our treatment methods may be simply converting early infantile into tardive prenatal syphilis.

Treatment of the Syphilitic Infant.—The syphilitic infant presents a very special problem in treatment and, in general, published reports have been marked by considerable pessimism as to results. The management of this phase of syphilis may be considered to have entered on a new era of possibilities with the recent development of bismuth and other forms of intramuscular medication. The child born with syphilis suffers the disadvantage of having been thoroughly saturated with organisms but possesses at the same time the coincident advantage of having, particularly if the infection occurred early in pregnancy, the opportunity to develop resistance under ideal conditions. The ability to survive after birth, therefore, depends quite largely upon the critical nature of the damage done by the disease. A child with a fibrous liver and fibrous lungs obviously has small chance of survival under any form of treatment. In general the writer believes that an **arsphenamine** and **bismuth** should be employed from the very outset in the treatment of prenatally syphilitic children rather than either drug alone. While the mercurial injunction still retains a place for prolonged and later treatment, mercury by mouth should be absolutely discarded in the treatment of the syphilitic infant. The use of bismuth alone has strong ad-

vocacy¹⁹⁹ but inasmuch as there appears to be no special reason why arsphenamine should be withheld, the general principles of synergism, control of infectiousness, and efficiency in the treatment of early syphilis (to which early prenatal syphilis is equivalent) would seem to require the use of both drugs, except in the presence of definite contra-indications.

The writer merely proposes from the various systems and dosage schedules available, two which should yield reasonably satisfactory results, the first using **sulpharsphenamine and bismuth**, and the second **bismuth arsphenamine sulphonate**, both these procedures being, of course, intramuscular. If the sulpharsphenamine-bismuth procedure is used, treatment should begin with sulpharsphenamine, 0.025 Gm. (0.375 Gr.) every third or fourth day, for three or four injections. The dose may then be cautiously increased to 0.050 Gm. (0.75 Gr.) every fifth day; and after about the eighth injection to 0.075 Gm. (1.125 Gr.), following from this point on the general rule effective in the experience of Boone and Weech, of an optimum dosage of 20 mg. per kilo. As soon as the interval between injections of sulpharsphenamine reaches seven days, bismuth may be given intramuscularly using any one of the acceptable salts of moderately rapid absorption, such as the salicylates. The bismuth injection should be given during the week between each two sulpharsphenamine injections, and under no circumstances should be substituted for the sulpharsphenamine itself, unless it is intended to transfer entirely to bismuth therapy, which the writer deems inadvisable, as already stated. The dose should not exceed 25 to 35 mg. of bismuth metal per week; the length of the sulpharsphenamine course should approximate 15 injections, and the bismuth course from 10 to 15 injections. The interval between sulpharsphenamine courses should be four to six weeks, this period being covered by the administration of bismuth. A total of 30 to 35 injections of each drug should be considered a minimum, if the tolerance permits. **Mercurial inunctions** may be used after the completion of the **sulpharsphenamine and bismuth** courses, but they should not be used during the sulpharsphenamine treatment. Exfoliative dermatitis seldom occurs in infants, but as already stated, sulpharsphenamine is distinctly uncertain in this particular and in the production of hemorrhagic accidents.

Bismuth arsphenamine sulphonate, while less intensive than the sulpharsphenamine-bismuth system suggested, is none the less a very satisfactory drug in the treatment of infantile syphilis. A dosage of 0.025 to 0.1 Gm. (0.375-1.5 Gr.) in a series of 40 injections at intervals of three to seven days is not excessive. Rest intervals not properly covered by bismuth treatment will result in relapses in the prenatal syphilis of infancy as in the acquired syphilis of adults. Fortunately the child responds to treatment better than the adult with reference to central nervous system involvement, but this does not do away with the necessity for a spinal fluid examination at the end of the second or perhaps the third year. It goes without saying that such a child must be kept under observation throughout life, that treatment may require renewal from time to time, that it can be prolonged by the use of inunctions and iodides at intervals and that bismuth intramuscularly is a particularly valuable aid in making sure that every last trace of the infection is reduced to inactivity. The general rule is that treatment should be continued for at least a year after the total disappear-

ance of every sign of the disease, both clinical and serologic, and that observation should extend to the thirtieth year or later.

The question as to whether treatment of the prenataally syphilitic child is capable of preventing reappearance of symptoms, including particularly interstitial keratitis and deafness in later years, cannot at this time be conclusively answered. It is much wiser to keep the child under observation with occasional serologic tests and to reinstitute treatment immediately upon the appearance of a partial or complete positive than to trust blindly to luck and to allow the child to escape from observation.

The syphilitic infant, particularly if cachectic, presents difficult nutritional problems and should not be removed from the breast if there is any way of avoiding it. The rapidity with which snuffles and mouth lesions are controlled by the modern methods of treatment solves a difficulty often present in the past.

Management of Tardive Heredosyphilis.—Tardive prenatal syphilis is late syphilis rather than early and, unless in the case of some fulminating complication, can be dealt with by the more leisurely but very persistent methods adopted for the later years of the acquired form. It is impossible to exaggerate the value of this leisurely but determined persistence in treatment in the securing of ultimate good results. In fact, if there is any criticism that can be made of the treatment of prenatal syphilis, it is that of a lack of persistence rather than an unwise choice of agents. Individual cases must, of course, receive the benefit of special measures. In the resistant case, as for instance, gummatous osteitis of the palate and septum, dosage may for a time tend toward the adult rather than the childhood scale. **Bismuth** alone can be used for months with highly satisfactory ultimate results, as pointed out by Wright.²⁰⁰ The writer has, he believes, been able to recognize a difference in favor of rapid effect between the soluble mercurial salts and the insoluble bismuth salts, which in his experience justifies the use of **mercuric succinimide** in the initial treatment of early cases of interstitial keratitis. Throughout the treatment of prenatal syphilis, as in the treatment of acquired syphilis, "**606**" **should be used where neoarsphenamine has failed** to produce results. This, of course, calls for the assistance of an expert. **Iodide** has a very definite place in the treatment of prenatal syphilis and may be given in huge doses in early interstitial keratitis or, for its tonic antisymphilitic effect, in small doses over broken periods of months for a total of years. As in the management of late syphilis, a spinal fluid examination is necessary to determine the freedom of the nervous system from involvement, and when such involvement appears a continuation or intensification of treatment produces favorable results even more frequently than in adults. On the other hand, juvenile paresis is highly resistant to treatment and the writer has yet to see a genuinely arrested case as a result of either tryparsamide or fever therapy. Fever therapy is rated by O'Leary and Brunsting as of no avail in these cases, but Osborne and Putnam¹⁹³ state that they have had excellent results in three cases.

Statistical evaluation of treatment results in prenatal syphilis cannot be based entirely upon serologic reactions, for reversal even under prolonged treatment may occur in only 50 to 60 per cent of certain types of cases. On the other hand, excellent clinical results can be obtained in 80 to 85 per cent of cases, the percentage being held below the hundred

mark by the occasional case of parietic neurosyphilis and the residua of interstitial keratitis. Particular emphasis should be placed upon treatment results by modern methods in interstitial keratitis. The duration of quite severe cases can be reduced by the simultaneous use of **arsphenamine and bismuth** with an intensity comparable to the treatment systems described for early syphilis from the usual period of six to eighteen months, to from two to six months, the rate of clearing of the cornea being seemingly less affected than the acute phase. It should be recalled that the use of small doses of neocarsphenamine at bi-weekly intervals without simultaneous use of bismuth, which seems to be common practice, is not regarded in this presentation as efficient treatment. Dealing with average material containing many cases which present high degrees of opacity and vascularization, the writer was able to secure favorable results in 66 per cent with marked improvement in 42 per cent. If the treatment of interstitial keratitis as practiced through the combined efforts of the Massachusetts Eye and Ear Infirmary and the syphilis clinic of the Massachusetts General Hospital (see Carvill¹⁰⁰) could be made universal, involvement of the second eye would become a comparative rarity and the residual damage which reaches so grave a figure at the present time could be reduced to almost negligible proportions. Osborne and Putnam¹⁰² were able to report noninvolvement of the other eye in 30 consecutive cases after intensive treatment was started.

Deafness in the prenatally syphilitic child does not respond to any appreciable degree to treatment.

The question of the fitness of prenatally syphilitic adults for marriage is frequently raised. The writer unhesitatingly subscribes to the belief that there are no contra-indications to marriage in a reasonably well-treated case. The possibility of a revival of interstitial keratitis following the strain of a pregnancy must, however, be borne in mind and accepted as a minor risk. Apart from a slightly increased tendency toward sterility, the prenatally syphilitic woman is no different from the average individual.

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CHAPTER XVII

GONOCOCCAL INFECTIONS

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History of gonorrhea, p. 451—Prevalence of gonorrhea, p. 452—Duration of gonorrhea, p. 452—Etiology, p. 453—Bacteriology, p. 453—Pathology of gonococcal infection, p. 460.

Gonorrhea in the male, p. 462—Symptomatology of gonorrhea in the male, p. 463—Diagnosis of gonorrheal infection, p. 468—Treatment of acute gonococcal urethritis, p. 476—Internal remedies, p. 476—Local treatment of urethritis, p. 479—Routine treatment of acute gonorrheal urethritis, p. 484—Prophylaxis, p. 489—Abortive treatment, p. 489—Treatment of chronic gonorrhea in the male, p. 490—Chronic anterior gonorrhea, p. 491—Chronic posterior gonococcal infection, p. 496—Chronic anteroposterior gonorrhea, p. 500—Acute exacerbations of chronic gonorrhea, p. 500—Complications of gonorrheal urethritis and their treatment, p. 500—Determination of a cure, p. 512.

Gonococcal infection in the female, p. 513.

Gonorrheal vulvovaginitis in children, p. 517.

History of Gonorrhea.—Gonorrhea, a Latin word of Greek origin, is first found mentioned in the writings of Aretaios of Cappadocia, a Greek physician who lived in the first or second century. There are several references in the earlier literature which justify the belief that the disease was prevalent long before this period. It probably existed among the early Egyptians because in the Papyrus Ebers, the oldest medical Egyptian record, are found prescriptions to be used as injections for venereal affections. There is also a very accurate description of gonorrhea in a Japanese manuscript of 900 B.C. That the Jews did not escape is proven by verses in the fifteenth chapter of Leviticus.

By the end of the sixth century, some conception of the inflammatory nature of urethral disease had evidently been developed, because mention is made of pyuria, hematuria and dysuria. Paul of Aegina speaks of urethral suppuration and bleeding without admixture of urine.

It was not until 1000 A.D. that any attempt to explain the etiology of the disease was made. Maimon, a Jewish physician at Cairo (1139-1204), includes lasciviousness and licentiousness among the various causes. Guillaume de Salicet, in the thirteenth century, attributed the disease to impurities retained under the prepuce after connection with an unclean woman. He was the first to suggest prophylactic washing.

In the fifteenth century we find the history of gonorrhea merging with that of syphilis. In 1530 Paracelsus taught that gonorrhea was an initial symptom of syphilis. This misconception held sway until overthrown by the excellent work of Ricord, begun in 1831 and continued until 1860.

The personal experiment of John Hunter, in 1767, still further strengthened this erroneous belief. He unfortunately contracted both syphilis and gonorrhea from an inoculation of impure gonorrheal pus. His prominence in the medical world caused his teachings to be widely accepted and it was not until the middle of the eighteenth century that Ricord succeeded in convincing the medical profession of the duality of gonorrhea and syphilis.

Prevalence of Gonorrhea.—In civil life, sexual promiscuity and prostitution make the disease endemic. Because of the nature of the disease, it is impossible to obtain accurate statistics. It is highly probable that every male who indulges in promiscuous intercourse sooner or later acquires a gonorrhea. According to Morrow, 60 per cent. of the adult male population of the United States have gonorrhea. Forchheimer places the figure at 51 per cent. Among women gonorrhea is less common than among men. Statistics show the proportion of men to women as 16 to 1.

In 1901, there were reported 162,372 patients suffering from venereal disease in New York City; of these 90 per cent. had gonorrhea. During the year 1907, more than 12 per cent. of the men in the U. S. Army had gonorrhea. In the Philippines the percentage was higher, 18.71 per cent. The duration of the disease varied from twenty-three to fifty days.

Duration of Gonorrhea.—Experience has shown that the duration of the disease varies within wide limits, depending upon its extent, complications, and the habits and general condition of the patient. It has been stated that in acute anterior urethritis the average recovery takes place in five to six weeks. Yet we constantly see cases of acute anterior urethritis complicated by a persistent folliculitis or periurethral abscess which may last from eighteen months to two years. As Ricord states, "We know when gonorrhea begins, but God alone knows when it will end." When the gonococcus invades the posterior urethra and prostate the infection may persist for even three years or more. In general, it may be stated that the gonococci usually disappear from the urethra in six months, and rarely persist for more than two years. It is exceptional for gonococci to be present after two or three years, although cases have been reported in which they were demonstrated after longer periods.

In women, it is much more difficult to form any opinion. Many competent observers are unwilling to set any limit to its infectiousness. Many women, like men, may recover in a few months. In others, the duration is much more indefinite and the disease much more rebellious to treatment. Cases of vulvovaginitis in children have been known to persist for years.

Etiology.—In the adult the disease is in practically all cases acquired by coitus. The gonococcus is implanted from an infected cervix or urethra into the urethra of the male, reaching, in all probability, the fossa navicularis to which for a time its location is limited. The epithelium of the fossa navicularis is of the squamous type and resistant to the gonococcus. The organism probably lives in the secretions of the canal and at this stage is therefore easily destroyed or removed by suitable prophylactic treatment.

Extraveneral infection in adults is extremely rare. Cases have, however, been reported in which infection was transmitted by infected towels, lavatory seats and urethral instruments.

The gonococcus may be inoculated in the eye, urethra and the female genital passages. The rectal mucosa is more resistant. All squamous epithelium offers marked resistance. The mouth and nose are practically immune except in young children. The preputial cavity, the vagina of the female, and the urinary bladder are rarely and only mildly involved in gonorrhea.

That children and infants are very susceptible to gonorrhea is evidenced by the frequency of vulvovaginitis and gonorrheal conjunctivitis. Nasal and buccal gonorrhea occur almost exclusively in children.

Bacteriology of Gonorrhea.—Neisser, in 1879, made the first successful attempt to find the causative organism of gonorrhea. He was the first to describe the microscopic appearance of the gonococcus as seen in urethral and conjunctival pus. Other observers confirmed his findings, but all attempts to grow the organism in artificial media failed until Bumm, in 1885, successfully used solidified serum derived from the human placenta. The separation of the gonococcus in pure culture enabled experimental inoculation to be undertaken in the human subject, and the successful issue of these operations demonstrated the direct causal relationship of the gonococcus to the disease.

MICROSCOPICAL APPEARANCE OF GONOCOCCUS.—The gonococcus is a diplococcus. In shape it is planoconvex or bean-shaped and the pairs lie with their concave or plane surfaces opposing. They have no capsule, form no spores and are non-mobile.

They vary considerably in size. In purulent secretions they are found both within and outside of the pus and epithelial cells. The most characteristic groups are met with inside the cells. There is no definite clinical relationship between the extracellular or intracellular position of the gonococci and the severity or stage of the inflammation, in a given case. In every specimen, gonococci are found both within and outside of the cells and in no definite proportion.

STAINING OF THE GONOCOCCUS.—The gonococcus readily stains with any of the basic anilin dyes, e.g., methylene blue, fuchsin, gentian violet, etc. It is easily decolorized with alcohol, acids, xylol and other reagents. Thus in staining by the Gram process the gonococci lose their violet color and take up a counterstain. They are, therefore, *Gram negative*.

Many special methods of staining these cocci are described, but the Gram method is by far the most important as it differentiates the gonococcus from all Gram-positive organisms. When the Gram stain is applied, a thorough washing with alcohol leaves the gonococci colorless, while pseudo-gonococci stand out in bold relief, stained darkly by the combined color of gentian violet and the Gram solution. In order to demonstrate more clearly the effect of the Gram stain, a contrasting counterstain (fuchsin, etc.) is employed in order that the gonococci may be visible by direct comparison with other organisms.

In following up the effect of treatment it is not necessary to use the Gram method of staining. A 2 per cent. aqueous solution of methylene blue makes a very efficient and rapid stain.

Preparation of the Specimen.—To prepare the smear in a suspected case of gonococcal infection in the male, cleanse the external parts. Transfer some of the discharge in the meatus with a platinum loop to a glass slide. If there is extreme tenderness of the urethra, a drop of secretion may be expressed from the canal and transferred to the slide by direct contact.

In the female the material should be taken from the urethra and cervix. In chronic and doubtful cases, attempts should be made to obtain the secretions from Skene's and Bartholin's glands. After cleansing the parts with sterile water, the urethral discharge is obtained as in the male. Frequently if no secretion is visible a drop may be expressed by inserting a finger in the vagina and firmly stroking the urethra from above, downward and forward. The cervix is then exposed with a speculum, and the external os wiped dry with cotton. A platinum loop is inserted into the cervical canal and the secretion placed on a glass slide.

The pus is spread on the slide in a thin film. Each slide is then dried by evaporation at a gentle heat and fixed by rapidly passing it three or four times through a spirit lamp or Bunsen burner flame.

Methods of Staining.—(1) *Methylene Blue*: The specimen is covered with a saturated solution of methylene blue for ten seconds, washed in running water, dried and examined with an oil immersion lens.

(2) *Gram's Method*: The solutions employed are:

A. Anilin-water gentian-violet. This consists of	
Anilin oil	3 c.c.
Absolute alcohol	7 c.c.
Distilled water	90 c.c.

Shake for two minutes. Filter until clear. Add two grams of Grüber's powdered gentian-violet. Set aside for twenty-four hours. Pipette supernatant fluid as required. This solution keeps well for 6 to 8 weeks. It takes time to prepare it, however, and it is quite unstable. The more stable carbolic-water solution of gentian-violet is recommended, consisting of:

- Saturated alcoholic solution of gentian-violet. 1 part
 Five per cent. solution of carbolic acid....10 parts
- B. Gram solution.
 Iodin 1 part
 Potassium iodid 2 parts
 Distilled water 300 parts
- C. Absolute alcohol.
- D. Contrast stain.
 Carbolic acid 2 parts
 Saturated aqueous solution of Bismarck brown 98 parts
 or
 Carbolfuchsin (Ziehl-Neelsen) 1 part
 Water 20 parts

Technic of Staining.—(1) Stain with anilin-water gentian-violet or carbol-gentian-violet for three minutes. Shake off excess of stain.

(2) Cover with Gram's iodin solution for two minutes.

(3) Decolorize with absolute alcohol for thirty seconds.

(4) Allow to dry.

(5) Counterstain with Bismarck brown or carbolfuchsin solution for three to five minutes.

Value and Limitations of Staining Methods.—For ordinary clinical work, the Gram method of staining is employed to distinguish the gonococcus from the staphylococci and other Gram-positive cocci. There are three sources of error, viz.:

(1) There are other Gram-negative cocci from which the gonococcus can be distinguished only by culture, such as the *Micrococcus catarrhalis*, *Diplococcus intracellularis* and certain chromogenic cocci. None of these organisms except the *Micrococcus catarrhalis* have been identified in the genito-urinary tract and none of them except the *Micrococcus catarrhalis* is believed to cause urethritis. The urethritis caused by the *Micrococcus catarrhalis* is rare and could not clinically be mistaken for acute gonorrhea.

(2) In a small percentage of cases in the normal urethra and also in the normal vagina, Gram-negative cocci are found. They can usually be differentiated from the gonococcus by their form, size and extra-cellular position.

(3) The fact that staphylococci may be Gram-negative as well as Gram-positive is a frequent cause of error.

These confusing factors apply almost exclusively to chronic urethritis. For all practical purposes, in cases of acute urethritis the presence of Gram-negative coffee-bean-shaped, intracellular diplococci is diagnostic of gonorrheal infection, when supplemented by the usual clinical evidence.

The methylene blue stain has no differential value. It is useful only because it is a quick method for studying the effects of treatment in a given case in which the diagnosis has previously been made by the Gram method. Neither the Gram nor methylene blue stain should be

relied upon to verify a cure of gonorrhea. *In order to establish a diagnosis beyond a doubt the isolation and identification of the specific organism is the only certain method.*

In acute cases, the gonococcus can usually be cultivated from the discharge without much difficulty, providing suitable culture media are employed. In chronic cases more difficulty is met with, and even when the greatest care is used in securing the material for examination and preparing the culture, repeated examinations are necessary before a definite opinion can be given.

In chronic cases or those in which a cure is to be determined, the method of obtaining material is as follows: The patient is instructed to report with a full bladder. After cleansing the parts with green soap and a 1-60 carbolic acid solution, the patient voids several ounces of urine into a sterile flask. The prostate and vesicles are then thoroughly massaged, after which the patient is instructed to void the remainder of the urine in a second sterile flask. The specimens, while warm, are immediately sent to the laboratory. Chilling of the samples reduces the chances of success. On the other hand prolonged exposure to body temperature permits the growth of other contaminating organisms which renders the isolation of the gonococcus more difficult.

For the initial culture of the gonococcus, either Wertheim's ascitic agar or Heiman's culture media is employed. For a detailed consideration of the preparation of the various culture media, and the cultivation and isolation of the gonococcus, the reader is referred to special works on the subject.

GONOCOCCAL IMMUNITY REACTIONS.—In addition to their scientific interest, the immunity reactions which can be excited by the gonococcus have an important practical bearing on certain methods of diagnosis. Their as yet incomplete development and interpretation have been due to the failure of all attempts to produce gonococcal infections in animals. No toxins seem to be elaborated by the gonococcus, but Wassermann and others have shown, by means of the complement-deviation test, that bodies similar to amboceptors were present in the blood of patients suffering from gonococcal infection. Since then much work has been done on the complement-deviation test, on opsonic action and agglutinations. The results, though far from complete, serve to substantiate the view that a specific immunity is elaborated in the human organism against the gonococcus.

Complement-Deviation Test.—The credit for having made the test of clinical value belongs to Schwartz and McNeil. The reactions depend upon the fact that, in the presence of the complement, gonococcal endotoxins (antigen) combine with gonococcal antibodies (patient's serum), and that, in doing so, the complement (guinea-pig serum) becomes "fixed" or "deviated." The fixation of the complement which occurs if gonococcal antibodies are contained in the patient's serum prevents lysis of the red cells and a "positive" reaction is then said to have been obtained.

According to Schwartz and McNeil, in cases of anterior gonorrheal

urethritis in the male, and acute vulvovaginitis in the female, a positive reaction is rarely obtained. When, however, the infection invades the posterior urethra in the male, and the cervix, glands of Bartholin and the pelvic organs in the female, the patient will react positively. The test becomes positive sooner or later in posterior urethritis, prostatitis, seminal vesiculitis, epididymitis, cystitis, pyelonephritis, arthritis, etc. A positive reaction persists six to eight weeks after a cure is effected. If a strong positive reaction persists *after* this period, the case should be regarded as still harboring gonococci.

(1) *Effect of Vaccines on the Test.*—If gonococcus vaccines are given to a patient with a fading or weakly positive test, the vaccines will change the weakly positive to a strongly positive test. If the patient has not recently had a gonorrhea, vaccines will have no effect upon the test.

(2) *Clinical Value of the Test.*—The accuracy of the test will vary according to the skill and experience of the serologist. Technical errors interfering with the validity of the test are much less likely to occur than in a gonococcus culture. On the other hand, a positive culture is more certain evidence that the gonococcus persists in the urethra or vesicles, than is a complement-fixation test. Thus if a patient has a gonorrheal arthritis as shown by a positive complement-fixation test, bacteriological examination is necessary to prove that gonococci are present in the urethra. On the other hand, the test will often help to differentiate between rheumatic and gonorrheal arthritis.

As previously stated, the results obtained will vary with different observers; thus Keyes made a careful comparison between the relative merits of the "fixation" test and bacteriological examination. In 100 cases, the complement-fixation test was wrong in 1 out of 47, the bacteriological test in 1 out of over 100 examinations.

In the authors' work, the test has proven of most value in acute posterior urethritis, prostatitis, vesiculitis, arthritis and systemic gonorrhea. A positive test means that gonococci are present in the body, bearing in mind that the reaction may persist from 6 to 8 weeks after a cure. In chronic gonorrheal prostatitis and vesiculitis, the results have not been so satisfactory, the test at times being negative when careful bacteriological examinations later demonstrated gonococci in urinary shreds or in the discharge.

In uncomplicated anterior urethritis, the test is of no value, a clear urine and negative bacteriological findings being necessary to determine a cure. In two clinic patients suffering from a hyperacute anterior gonorrhea, one complicated by periurethral abscess and the other by balanoposthitis, a positive fixation was obtained.

In conclusion it may be said that a positive fixation test signifies the presence of gonococci in the body. A negative test is not so reliable. This fact must be borne in mind when the test is employed in the determination of a cure. Variations in the different strains of gonococci may probably explain some of the misleading negative reactions and the per-

sistence of antibodies in the blood after all gonococci have been exterminated may account for erroneous positive results.

Gonococcus Vaccines.—Either stock or autogenous vaccines are employed in the treatment of gonorrhea. Autogenous vaccines have the advantage of being specific in a given case. They have the disadvantage, however, in that it takes several days to prepare them and are, therefore, not available when needed. The experiments of Teague and Torrey showed that the serum of an animal immunized to one strain of gonococcus did not cause fixation of complement when tested against an antigen obtained from another strain. They were able to differentiate eleven strains of gonococci. Most of the stock vaccines now sold are a mixture of different strains and are commonly employed when beginning the treatment.

(1) *Dosage.*—This varies with different urologists from 10,000,000 to 50,000,000. We usually begin with 50,000,000 and increase 25,000,000 at each dose until a maximum of 200,000,000 is reached. The injections are given intramuscularly, preferably in the gluteal region, and are not repeated oftener than every other day.

Local pain and inflammatory reaction following injection are usually mild. General febrile or toxic reactions sometimes occur, if the dosage is high or pushed too rapidly. They rarely last more than twelve hours.

(2) *Results.*—In acute or chronic urethritis and vulvovaginitis we have never seen any benefit derived from the use of vaccines. In acute prostatitis, epididymitis, vesiculitis or periurethral lesions, the employment of vaccines frequently seems to lessen the severity and duration of the disease. When a patient with gonorrhea develops fever or symptoms suggestive of these complications the prompt use of vaccines may perhaps abort them. In systemic gonorrhea, many authorities rely upon frequent injections ranging from 50,000,000 to 600,000,000. In gonorrheal sepsis the results are sometimes very definite, in others they are entirely negative.

Antigonococcus Serum.—Rogers and Torrey employ a polyvalent serum obtained from the ram. It is also prepared from rabbits, sheep and horses. The serum of the former is preferred because it seems less toxic. The animals are immunized by injections of increasing doses of gonococcus emulsion. The serum is tested for its gonococcus antibody content by means of the complement-fixation test.

(1) *Dosage.*—This varies from 2 c.c. to 25 c.c. at 24 to 48-hour intervals. When ram serum is used, a local reaction may occur, characterized by a varying amount of swelling, redness and tenderness.

(2) *Results.*—In localized gonorrhea and its complications, the results are variable and perhaps inferior to those of the vaccines. In systemic gonorrhea and in joint cases, Rogers reports good results in 85 per cent. of early cases. Herbert reports satisfactory results in all chronic joint cases. Swinbourne states that when the serum was employed at the onset of 27 cases of acute epididymitis, the pain was relieved in 24 hours. Watson has employed it in the vaginitis of children without result.

BACTERIOLOGY OF CHRONIC GONOCOCCAL INFECTION.—*Chronic Urethritis.*—The existence of a mixed infection, in chronic urethritis, is due, in most cases, to the various types of bacteria which are found under normal conditions in the urethra. In a general way, it may be stated that chronic urethritis may be due to:

- (1) The persistence of the gonococcus.
- (2) Presence of the gonococcus in conjunction with other bacteria.
- (3) Other bacteria without the gonococcus.

As previously stated, the gonococcus in the male is rarely found after three years. Notthaft, who states that the gonococcus always disappears from the prostate within three years, is supported in his belief by Finger, Wassidlo, Goldberger, Neisser, Frank and others. The bacteria in normal urethrae have been studied by various observers. Pfeiffer examined 24 normal subjects and found diphtheroid bacilli in 21, streptobacilli in 10, *Staphylococcus pyogenes aureus* in 5, *Micrococcus candidans* in 4, *Sarcina alba* in 14. Petit and Wassermann found 5 varieties of cocci, 6 kinds of bacilli. Franz, in 56 urethras, found the sarcina once, *Bacillus coli communis* once, *Staphylococcus pyogenes* 6 times, streptococci twice, and 7 other varieties of cocci and four of diplococci. These bacteria were found, in practically all cases, near the meatus. Very few, or none, were found in the deeper portions of the anterior urethra.

Chronic Anterior Urethritis.—In 154 cases, examined by Tano, Cohn, Owens and van Hoffmann, 10 showed gonococci alone, 10 gonococci mixed with other bacteria, 114 other bacteria without gonococci; 20 were sterile.

Chronic Prostatitis.—Young, Geraghty and Stevens examined 17 cases. They obtained a growth on agar in only eight. The staphylococcus was found in 3 and *Streptococcus pyogenes* in 2. Notthaft examined 120 cases. He found the gonococcus 47 times, other micrococci, 119, bacilli, 15, other bacteria, 14 times. Cohn in 12 cases found *Staphylococcus albus* 11 times, streptococcus 3 times, bacillus coli once, other bacteria 3 times, no gonococci. The gonococcus was not found after the third year. He found the gonococcus in only five cases within 18 months of the time of infection. In cases of less than 18 months, the gonococcus was found in 60 per cent., either alone, or with other bacteria. In cases ranging from 18 months to 2 years, the gonococcus was found in 18 per cent. Cases of from 2 to 3 years' standing showed gonococci in 6 per cent.

Chronic Vesiculitis.—Gonococci are rarely found. Cultures are often sterile. The usual bacteria present are staphylococcus, streptococcus, *Bacillus coli communis* and *Bacillus lactis aerogenes*.

INCUBATION PERIOD.—This varies from two days to two weeks. The average incubation period is from 5 to 7 days. In inoculation experiments the incubation period is from 2 to 5 days. The shortest incubation periods are probably due to a combination of simple urethritis or sexual strain with gonococcal infection. Exacerbations develop, as a rule, more quickly than new infections.

According to Keyes, the average incubation period of 34 primary attacks was 6 days. Of these the primary attack in 20 per cent. appeared before the fifth day, in 61 per cent. on the fifth, sixth and seventh days. In 76 secondary attacks, the average incubation period was 4.88 days, of which 55 per cent. appeared before the fifth day, and 31 per cent. from the fifth to the seventh day.

Pathology of Gonococcal Infection.—Wherever the gonococcus is found, tissue changes characteristic of bacterial invasion are soon apparent. The organism at first grows on the surface of the epithelium, forming surface colonies. The production of toxins by the gonococci soon causes hyperemia and serous exudation. The cylindrical epithelial cells become swollen and loosened and cast off in great numbers. The smaller blood-vessels are seen crowded with leukocytes, and diapedesis and leukocytosis are soon in active process, causing the characteristic purulent discharge. The concentration of the wandering cells is greatest immediately below the epithelial layers.

Squamous epithelium is more resistant to the gonococcus and, although colonies may flourish on the surface, they do not penetrate between the interstices of the cells. In the case of cylindrical epithelium, gonococci readily reach the corium and, frequently, also the submucous tissue. Wherever the gonococci penetrate, there is intense infiltration in proportion to the number of organisms. As the gonococci pass along the lymph-channels, they set up more or less lymphangitis. As the purulent stage subsides, the denuded areas of epithelium are regenerated and layers of flattened cells are formed.

ACUTE ANTERIOR URETHRITIS.—We are indebted to the writings of Finger, Gohn and Schlagenhauser for the pathological findings in acute anterior urethritis. The urethra of condemned criminals were inoculated, and immediate postmortem examinations were made to investigate the various stages of invasion of the tissues by the specific microbe. Thirty-eight hours after inoculation, the gonococci had only just begun to penetrate between the epithelial cells. At the end of three days, the surface of the epithelium was covered with pus, the epithelium being infiltrated with bacteria on one side, and by leukocytes on the other. The inflammatory changes showed striking characteristics:

- (1) The squamous epithelium of the fossa navicularis resisted the invasion of the gonococci almost absolutely.

- (2) The cylindrical epithelium of the penile urethra showed extensive invasion, most marked about the crypts and glands, which were packed with pus and gonococci.

- (3) The subepithelial connective tissue contained few gonococci, except in the neighborhood of glands and crypts. Definite inflammatory changes, however, were present.

The glands and crypts are implicated in the general inflammatory process and form important centers of inflammation. Their orifices frequently become closed by the swelling of the mucous membrane. Since the gonococci often extend to, and sometimes into, the corpus spongiosum, the suppuration and periglandular infiltration arising is

often very intensive and extensive at the height of an acute gonorrhea.

CHRONIC ANTERIOR URETHRITIS.—There is a distinct tendency in a considerable proportion of cases for the processes which are productive of cure to stop short of completeness, causing a so-called chronic inflammation, which allows the gonococcus to maintain its existence in certain areas, although its activities are restrained. The following pathological changes are noted:

(1) The periglandular inflammatory exudate is gradually converted into cicatricial tissue. The extent and density of the connective tissue formation will depend upon the intensity and distribution of the acute inflammation.

(2) Changes in the glands and crypts are seen. The inflammation within them may persist, resulting in the "glandular urethritis of Oberlander." The opening of the gland may become occluded, causing the formation of a purulent or colloidal cyst (dry urethritis of Oberlander). The inflammation may cease, either by a return to the normal, or by cicatricial obliteration of the gland. These changes may all be seen in the urethra at the same time.

(3) Changes in the mucous membrane are those of chronic inflammation. They may be general, or localized over one or more small areas. The type of inflammation will depend upon the degree of infiltration and sclerosis. If the sclerosis is slight and infiltration predominates, the urethroscope shows the surface to be swollen, red and eroded in spots, while here and there appear the inflamed orifices of suppurating glands. This stage has been termed the "soft infiltration of Oberlander." When there is marked sclerosis, the overlying mucous membrane is lighter in color than the adjacent healthy mucosa and appears salmon-colored or dirty grayish yellow. Elsewhere there may be ulcerations, erosions, papillary outgrowths, with here and there a patch of squamous epithelium. This is the "hard infiltration of Oberlander." When the sclerosis is still more marked and extensive, urethral stricture results, diminishing the caliber of the urethra. The soft infiltration may heal spontaneously by absorption; the hard infiltration requires dilatation and leaves a permanent scar.

MEMBRANEOUS URETHRA.—Inflammation of this portion of the urethra is clinically mild. Submucous infiltrations are usually slight and stricture is rare. The glands are relatively few and simple and chronic glandular catarrh is comparatively mild.

PROSTATIC URETHRA.—In this part of the canal the glands are large and complex. Gonococcal infection often causes abscesses in the glands which break through into the canal. The verumontanum and sinus peculiaris may also be the seat of abscess formation.

THE PROSTATE.—When the prostatic urethra is involved there is practically always some involvement of the prostate. Prostatitis is perhaps the most frequent and important complication of genital gonorrhea in the male. In the milder forms, the inflammation extends into the ducts and either spares or does not markedly involve the acini (catarrhal prostatitis), with very little or no infiltration of the stroma. When the

acini are involved they become distended with pus, with infiltration of the surrounding stroma. When the inflammation becomes chronic, the involved acini may continue to suppurate or become cystic, necrotic or atrophic, with induration of the interstitial tissue (follicular prostatitis). When the inflammation is more intense, there is a more marked involvement of the stroma. Abscesses may form in small multiple foci, few or many of which may resolve or coalesce to form a large abscess, which usually ruptures into the urethra or, more rarely, into the ischio-rectal fossa or rectum.

CHRONIC PROSTATITIS.—According to Young, Geraghty and Stevens, the microscopic changes are as follows:

“Periacinous infiltration is the essential lesion of chronic prostatitis. This frequently exists alone or may be combined with interstitial and endoglandular processes. The changes in the acini are manifold. In some instances the cul de sacs are dilated; this dilatation may be due to stricture or obstruction in the excretory ducts, but it is probably more often the result of an accumulation of inflammatory products in the glandular sacs, the muscular tone of whose walls has been injured by the inflammatory process. Acini, however, the caliber of whose lumina has been diminished, are almost as frequently seen as are dilated ones, and this is especially true where the prostatitis has been of long standing and an extensive periacinous sclerosis has formed. At times the acini are mere vestiges or may be entirely replaced by fibrous tissue in areas of considerable extent. The acini are often partially or entirely filled with proliferating and desquamated epithelium.”

SEMINAL VESICULITIS.—In acute gonorrhoea the vesicles undergo the same changes as are found in the prostate. Abscess of the vesicles is rare. In chronic inflammation the walls of the vesicles are infiltrated. In severe cases or in those of long standing, a perivesicular infiltration is often found. As the condition becomes more chronic, the round-cell infiltration becomes organized and contracts, causing occlusion of the lumen. The gland does not drain and frequently in long-standing cases the vesicle, instead of being a branched ramifying canal, is converted into an irregular cavity containing pus.

GONORRHEA IN THE MALE

When gonococci are implanted upon the urethral mucous membrane, they multiply and produce an inflammation which, under favorable conditions, may terminate in the anterior urethra without invading the posterior urethra. Usually, however, after the organisms have been multiplying for some time in the anterior urethra, they gradually extend backward and invade the posterior urethra. The inflammation may invade the prostatic ducts and infect the prostate, or it may involve the seminal vesicles by extension through the ejaculatory ducts, or by further extension downward through the vasa deferentia, invade the epididymes and testicles. Although the organisms may reach the bladder

by the back flow of pus from the deep urethra, the latter is rarely involved. The same is true for the ureters and kidneys. Although it is quite possible for these organs to be involved by direct extension, the hematogenous route is in all probability the usual route. Once the posterior urethra and prostate are invaded the organisms may find their way into the blood stream and give rise to metastatic lesions.

In describing gonorrhea and its complications, we should, strictly speaking, consider anterior gonorrheal urethritis as the essential condition and class all other gonorrheal inflammations, including posterior urethritis, as complications; because under favorable conditions gonorrheal inflammation of the anterior urethra may terminate, as such, without involving the deep urethra. In the average gonorrhea, however, the deep urethra is usually involved. In as much as the symptomatology of anterior urethritis differs so much from that of posterior urethritis, it is clinically more convenient to consider them separately in the type description of the disease and to consider other gonorrheal inflammations as complications of one or the other. Accordingly, we shall describe in the course of this article:

(1) *Acute anterior gonorrheal urethritis:*

Complications: Abscess of urethral glands.
Periurethral abscess.
Inflammation of erectile tissue.
Balanoposthitis.
Adenitis.

(2) *Acute posterior urethritis:*

Complications: Prostatitis, Prostatic abscess.
Seminal vesiculitis.
Epididymitis.
Pyelitis, Pyelonephritis.

(3) *The metastatic lesions include:*

Bacterial lesions: Arthritis.
Endocarditis.
Iritis.
Bursitis, Tenosynovitis.
Periostitis, Osteitis.
Myositis.

(4) *Rare forms:*

Anorectal gonorrhea.
Buccal gonorrhea.
Nasal gonorrhea.

SYMPTOMATOLOGY OF GONORRHEA IN THE MALE

Acute Anterior Gonorrheal Urethritis.—In the beginning a slight tickling itchy irritation is felt at the meatus. The lips may be adherent, or a small amount of bluish sticky discharge may be seen between them.

A slight burning or stinging on urination is next experienced. This may last a day or two, when the meatus begins to swell and redden. The discharge increases in amount and becomes frankly purulent, varying in color from a creamy yellow to a greenish color. The *symptoms* are:

- (1) Swelling of the meatus.
- (2) Purulent discharge.
- (3) Painful urination.
- (4) Chordee.

(1) *The Meatus*.—At first the meatus is glued together, later the lips are red, swollen and everted and in very severe cases eroded. To the experienced observer, this appearance of the urethral orifice is almost pathognomonic of gonorrhea. Usually by the end of the second week, the swelling and redness subside and disappear, long before the inflammation in the deeper parts of the canal has terminated. In secondary attacks, and in acute exacerbations of chronic urethritis, the involvement of the meatus is less constant and less marked.

(2) *The Discharge*.—This at first is serous and opalescent, later as pus is formed it assumes a milky color. When the inflammation is at its height, it consists of greenish yellow pus, occasionally streaked with blood. In the subsiding stage, the pus ceases to be thick and gradually becomes paler in color, finally diminishing in amount and becoming more watery in quality.

(3) *Painful Urination*.—The passage of urine is painful and slow and somewhat obstructed, because the mucous membrane is swollen, eroded and sensitive. The pain on urinating reaches its height usually by the end of the first week and begins to subside after the second week.

(4) *Chordee*.—Chordee or painful erections are of frequent occurrence. The irritation produced by the inflamed mucous membrane causes erections, especially at night. The infiltration of the urethral mucosa and spongy tissues of the corpus spongiosum renders them relatively inelastic, hence the stretching of the tissues during erections becomes exceedingly painful. The corpora cavernosa retain their elasticity so that when the penis is erected it is curved downward.

Examination of the Urine.—The urine voided into a glass appears turbid. This turbidity is due to pus, mucus and desquamated epithelium. As the case goes on to recovery the urine gradually becomes clearer and finally transparent, containing filaments or so-called "clap shreds." These latter, on microscopic examination, are seen to be made up of pus cells, desquamated epithelium and mucus, with or without gonococci. Their presence indicates that isolated eroded portions of mucous membrane are not covered with epithelium and are still secreting pus.

The "two-glass urine test" should be made at each visit to determine:

A. The amount of pus excreted.

B. Whether the posterior urethra is invaded.

The diagnostic value of the so-called "glass tests" will be discussed later.

Examination of the Smear.—Although in rare instances, about 1-5000, the *Micrococcus catarrhalis* may be the exciting cause, the finding of a Gram-negative intracellular diplococcus, in conjunction with the characteristic clinical signs, clinches the diagnosis for all practical purposes. Only in medico-legal cases is a culture necessary.

At the onset of the disease, the smear shows quantities of desquamated epithelium, pus cells and mucus. Clumps of intracellular and extracellular gonococci are seen.

At the height of the inflammation the pus cells predominate and many gonococci are present.

During the stage of decline the pus cells are diminished in number and fewer of them contain gonococci. Epithelium is present in larger amounts. As the case goes on to a cure, the gonococci disappear and the discharge or urinary sediment contains only desquamated epithelium, mucus and an occasional pus cell with no gonococci. It is rare for the gonococci and pus to disappear within six weeks. They usually persist from 8 to 12 weeks.

The methylene blue stain should be used as a routine method during the course of the disease to determine the efficacy of the treatment.

Acute Posterior Gonorrheal Urethritis.—The frequency with which posterior urethritis develops in acute gonorrhea varies with different observers from 60 to 90 per cent. This variance is probably due to the type of patients studied. Among the laboring classes, such as frequent the clinics, the percentage of posterior involvement is undoubtedly higher. Prostatitis is estimated to complicate from 70 to 80 per cent. of the cases of acute posterior urethritis.

Posterior urethritis usually develops between the seventh and fourteenth days.

The *symptoms* of posterior invasion are all referable to acute inflammation of the vesical neck, as is also the appearance of pus in the second flow of urine.

(1) *Frequency and Urgency of Urination.*—Because of the acutely inflamed hypersensitive condition of the mucous membrane of the prostatic urethra and trigon, the accumulation of relatively small amounts of urine in the bladder causes an intense desire to urinate. This may be so great, in severe cases, that the patient dribbles away a few drops of urine every 15 minutes. In anterior urethritis the patient urinates as infrequently as possible, in order to escape the pain of urination. In posterior urethritis the call to urinate is so imperative that *he must urinate*. The frequency and urgency is present during the night, although less marked than in the daytime. Yet it may be intense enough to cause a sleepless night, unless measures are taken to relieve it. In the milder cases there may be practically no frequency or urgency.

(2) *Painful Urination.*—The pain on urination in posterior urethritis is very characteristic. It may be referred to the perineum, rectum, epigastrium or to the anterior urethra. It appears just before the act in the form of urgency. During urination it may be felt either in the

perineum, rectum or anterior urethra, but it is toward the end of the act that it is felt most acutely. The contractions of the bladder and urethra in attempting to expel the last drops of urine, cause a series of spasmodic pains which may persist for several minutes, even after the bladder has emptied itself.

(3) *Terminal Hematuria*.—This is caused by the terminal spasm. In severe cases the last jet of urine may be almost pure blood. In mild cases it is not present. The bleeding may be constant or intermittent. In either case the amount of blood lost is not great.

(4) *The "Two-Glass Test."*—In acute posterior urethritis the pus which forms in the deep urethra flows back and becomes mixed with the bladder urine. The second urine voided is therefore always turbid.

Chronic Gonorrhea.—By common consent a gonorrhea of less than two months' duration is called acute. When it persists for more than three months it is considered chronic. This distinction is purely an arbitrary one and serves to emphasize the fact that while in some cases gonorrhea may be cured in two months, in others there is unfortunately a distinct tendency for the processes which bring about a cure to stop short of completeness and for the gonococcus to maintain its existence in certain areas, either alone or in conjunction with other organisms.

In chronic gonorrhea, gonococci are most frequently found in gland ducts, either in the anterior urethra (gonorrheal folliculitis), or in the posterior urethra (chronic gonorrheal prostatitis). They may also survive for some time in the mucosa. In either situation it is difficult to reach them with any local antiseptic. In the presence of continuous irritation, the surrounding infiltration, usually of periglandular localization, instead of becoming absorbed, undergoes a series of changes, resulting eventually in the formation of cicatricial tissue. Clinically the different stages are recognized as "soft" and "hard" infiltrations. The final end result in unfavorable cases is stricture.

In order to distinguish the symptoms of anterior urethritis from those of posterior, both conditions must be studied separately. Clinically, however, the two usually exist together, either one or the other predominating.

CHRONIC ANTERIOR URETHRITIS.—Chronic anterior urethritis is characterized by:

- (1) Urethral discharge.
- (2) Tendency for acute exacerbations.
- (3) Pain, itching or burning in the urethra.
- (4) Urinary signs.

(1) A *urethral discharge* is the one subjective symptom of chronic anterior gonococcal urethritis. It varies in quantity, and is purulent, mucopurulent or mucoid in appearance. At times the discharge is profuse, at others it is very scant or may not show at the meatus, simply appearing in the urine in the form of urinary shreds. In others, owing to the more frequent flushings of the urethra with urine during the day, no discharge is seen, but over night sufficient discharge collects and appears as a "morning drop."

(2) *Acute exacerbations* may occur during the course of a chronic anterior urethritis, simulating a new infection. The outbreaks are usually much less severe than the initial attack. They may come on without any apparent cause, or they may follow erotic excitement, sexual or alcoholic excesses, in which case they appear suddenly and subside rather quickly.

(3) *Pain*.—This is rarely felt in chronic urethritis unless an acute relapse occurs, in which case it is rarely so severe as in the initial attack. Usually, the patient complains of itching, slight soreness or burning in some portion of the urethra. The site of the pain is usually located just behind the glans penis.

(4) *Urinary Signs*.—These constitute an important element in the diagnosis and will be discussed later.

STRICTURE.—This very important complication will be considered separately.

CHRONIC POSTERIOR URETHRITIS AND CHRONIC PROSTATITIS.—Chronic posterior urethritis is always complicated by some involvement of the prostate. In fact, it is clinically impossible to differentiate one from the other. Hence it is preferable to consider chronic posterior urethritis in conjunction with chronic prostatitis.

The *symptoms* of chronic inflammation of the posterior urethra and prostate as classified by Young are as follows:

(1) The urinary symptoms are urethral discharge, disturbances of urination and mechanical obstruction to urination.

(2) The referred symptoms are reflex pains and abnormal sensations.

(3) The sexual symptoms are sexual disturbances, spermatorrhea and prostaticorrhea.

(1) *Urinary Symptoms*.—If no anterior inflammation is present, then no urethral discharge is seen. Since, however, posterior inflammations complicate about 80 per cent. of chronic anterior urethritis, the patient's complaint of a persistent discharge should warn the physician of the possibility of an accompanying posterior inflammation, because such urethral discharges can only be cured by the combined treatment of the anterior and posterior inflammations.

Urination may be normal, or there may be frequency and urgency of variable intensity. At times there may be pain before or during the act. Although urinary obstruction is infrequent, the stream may be weak, slow to start, with more or less dribbling. This may be due to turgescences of the mucosa of the deep urethra, swelling of the verumontanum, the formation of a median bar or to cicatricial contraction of the vesical neck. The symptoms in the more marked cases are those of prostatism in a young person, without enlargement of the prostate as felt by rectum.

(2) *Reflex Pains*.—The characteristic pains of chronic posterior urethritis and prostatitis are in the back, above the pubis, in the perineum, in the groin, testis, or along the urethra.

Pain in the back is usually felt in the sacrum and lower lumbar vertebra, rarely over the kidneys. It may be a constant dull ache or may be most pronounced in the morning, disappearing during the day.

Erotic excitement, repressed sexual desire or excesses tend to aggravate it. In one of our patients, a physician, the pain was most marked at night, and was intense enough to cause insomnia. This was promptly relieved when local treatment of the prostate was begun.

Perineal Pains.—These may be mild or very annoying. The patient is usually nervous and irritable. He cannot sit in one position for any length of time, but shifts about continuously to relieve the symptom, which is evidently due to continued pressure against the perineum. He frequently complains of a dull ache, burning or sense of fullness in this region.

Urethral Pains.—These may be present in the perineum or they may be referred to a point just behind the glans or to the penoscrotal junction. In some cases a numbness of the glans is complained of.

(3) *Sexual Disturbances.*—These are nearly always present. The sexual appetite is disturbed. There may be a constant desire for intercourse which is not satisfied by indulgence, or there may be no inclination for coitus which, if indulged in, is followed by a condition of general nervous depression. Premature ejaculation occurs on account of the hypersensitive, irritable condition of the posterior urethra and, for the same reason, nocturnal emissions may occur. As the condition advances, erections cease entirely and impotence is the final result.

Prostatorrhea and Spermatorrhea.—As a result of chronic inflammation of the prostate, functional disturbances, such as urethrorrhea, prostatorrhea and spermatorrhea are frequently encountered. Unless the case is of long standing proper local treatment and a carefully regulated sexual hygiene corrects them in time.

CHRONIC GONORRHEAL VESICULITIS.—Chronic vesiculitis is always associated with chronic prostatitis and posterior urethritis. In addition to the sexual symptoms noted above the following may be complained of when the vesicles are involved.

Rectal Pains or Vesicular Colic.—These are felt high up in the rectum, and are usually spasmodic and griping in character. They may be brought on by erection, straining at stool, ejaculation, or may occur spontaneously. Sometimes the pain is felt so high up that it simulates renal colic.

Painful Testicle.—Neuralgia or irritability of the testicle may be due to a reflex pain from a corresponding diseased vesicle. It consists of a sensitiveness of the whole gland or some portion of it. Mere contact of the clothing may be exquisitely painful. When vesiculitis is the cause, treatment will relieve the condition.

Gonorrheal Rheumatism.—Fuller first suggested that chronic seminal vesiculitis was the cause of gonorrheal rheumatism. This will be considered under rheumatism.

DIAGNOSIS OF GONORRHEAL INFECTION

In the diagnosis of gonorrhea involving the lower urinary tract and the genital organs in the male, two essential features are necessary:

(1) Discovery of the gonococcus; (2) diagnosis of the seat of the lesion: first, in acute urethritis, second, in chronic urethritis.

It is advisable to have some routine method when patients present themselves for examination, otherwise important features may be overlooked.

The writers have found the following method most practical and suitable for both private and clinic practice:

History of the Case.—A careful history is taken; this includes:

Past History	{	Number of previous attacks.
		Duration of previous attacks.
		Complications.
		Condition after treatment.

Present History	{	Duration.	
		Incubation.	
		Discharge.	
		Pain (character, location).	
		{	Character of urination (force, quantity, frequency, precipitancy, tenesmus, dribbling, hesitancy, etc.).

Examination of Male Patient Standing.—EXTERNAL GENITALS.—

The size, shape or malformations (hypospadias, epispadias, etc.) are noted. The condition of the glans and prepuce and the presence or absence of ulcerations, verrucae, abscesses, lymphadenitis, etc., are next determined.

The *meatus* is next inspected. Its size and shape are noted. If there is a urethral discharge, a smear is taken for microscopic examination. If the discharge is scanty, it is sometimes possible to obtain a sufficient amount by pressing upon the urethra from behind forward. If there is an induration at the meatus with the lips pressed together it may indicate the initial lesion of syphilis, whereas if ulceration is present, chancreoid may be the cause. Ulceration with induration associated with a thin bloody discharge may mean either syphilis with mixed infection or a cancerous lesion originating in the urethra (in the aged). If the lips of the meatus are red, swollen and exude a creamy discharge, then gonorrhea is the most probable cause. To confirm this and to afford the patient the advantages of early local treatment, the microscope is necessary for immediate diagnosis.

The Urine.—The patient passes a portion of his urine into a glass cylinder. The color, transparency and presence of shreds and mucus are noted.

He is then asked to void a second portion of urine, retaining some in his bladder. The second urine is inspected the same way.

PROSTATE AND VESICLES.—This is a very important part of the examination and should never be omitted, otherwise important information of the nature, extent and chronicity of the disease may be missed. The

patient bends forward, resting his hands on a table. The examiner places a finger cot on his forefinger, lubricates it with vaselin and inserts it in the rectum. By placing the fingers of the left hand in the groin of the patient and making counterpressure, the vesicles can be more easily palpated. Some urologists advise first distending the bladder with boric acid solution. This is not necessary and is employed only in subjects with narrow pelvic outlet, in which the prostate and vesicles seem high up, out of reach of the finger.

The examiner notes the shape, size, consistency and tenderness of the parts. Gentleness is essential. Rough, jerky movements frighten and hurt the patient, making him strain and rendering the examination useless. An intensely hot, swollen, tender, enlarged, turgid gland with one or both lobes involved points to acute prostatitis. Nodules in the prostate show local areas of follicular inflammation, either gonorrheal, simple chronic or tuberculous.

A prostate which is soft and boggy indicates chronic atonic prostatitis. An enlargement of the gland with nodular swellings, indurations and depressions, without acute symptoms, points to tuberculosis. In elderly men an enlargement denotes hypertrophy or malignancy or both. When the prostate is small, irregular in outline with depressions and soft areas, it signifies that former abscesses have destroyed a part of the prostatic tissue.

Normal vesicles cannot be outlined when empty. In young vigorous adults who practice continence or indulge rarely in intercourse, varying degrees of distention are met with. This does not necessarily imply disease. In acute inflammations the vesicles are engorged, thickened and tender. Distended tender vesicles point to a sub-acute process or to congestion with retention of vesicular secretion.

In chronic inflammations, the vesicles may have thickened or atonic flabby walls. They may be nodular or irregular in outline due to scar formation or stricture. Small, stringy, hard and irregular vesicles are the result of chronic inflammation with partial destruction.

The Third Urine.—During the examination of the prostate and vesicles the organs are gently massaged with the finger, after which the patient is told to void his urine in a third cylinder. The three urines are then examined separately for bacteria, pus, mucus and epithelium. The first urine contains the washings of the urethra plus any elements from the bladder, ureters and kidneys. The second represents that from the bladder, ureters and kidneys alone, *assuming that sufficient urine was passed in the first portion to flush out the urethra.* The third urine contains, in addition to the second urine, the products massaged from the prostate and vesicles.

The careful microscopic examination and comparison of these urines often give valuable information to the surgeon regarding the nature and intensity of the pathological process. They should not, however, be solely relied upon to *localize* inflammatory processes in the anterior and posterior urethra or in the prostate and vesicles.

Many physicians have the erroneous impression that the first urine

voided represents the contents of the anterior urethra, the second that of the posterior urethra. In reality the first portion voided washes out the discharge present in both the anterior and posterior urethra. In acute anterior urethritis pus forms only in the anterior urethra. In acute anteroposterior urethritis, pus, in addition, accumulates in the deep urethra and becomes mixed with the bladder urine and makes it turbid. Therefore, in all acute urethral inflammations, if the first portion voided is cloudy and the second portion is clear, it is reasonable to assume that the inflammation is confined to the anterior urethra only. When both urines are turbid (excluding phosphaturia) then, in all probability, anteroposterior inflammation is present. It is important to have the first portion voided a generous one, to avoid incomplete flushing out of the anterior urethra, otherwise the second urine will contain the pus left behind and incorrectly indicate posterior involvement. It will be seen from the foregoing that in *acute* urethritis the two-glass test is of most value in determining the extent of the involvement.

In subacute and chronic urethral and prostatic involvement the problem becomes more difficult, thus:

In chronic anteroposterior inflammations the amount of discharge present in the deep urethra may be so scant that none flows back into the bladder. The first portion voided is very apt to flush out the whole canal, while the second portion is clear, giving the examiner the impression that the discharge comes only from the anterior urethra, which is wrong. In these cases, where pus formation is scanty, the so-called "comma shred," which is derived from the opening of the prostatic ducts, will often help the surgeon to localize the lesion. These shreds are usually most abundant in the first specimen, and if the second urine is looked at when freshly voided, a number of them will invariably be found.

From the foregoing we have seen that these tests are not exact. A great many other "glass tests" have been devised, involving the use of three, five, seven and even nine glasses, in an attempt to localize the inflammation in the anterior and posterior urethra and prostate and vesicles exclusively. Experience has shown that this multiplicity of glass tests is of no practical value. In chronic cases, where the discharge consists only of shred formation, and where doubt exists as to their source, the following method is of value.

The patient is told to report with a full bladder. He is placed on the treatment table and the anterior urethra is flushed out with one quart of sterile water. This is collected in a basin and labeled "Specimen No. 1."

He then voids part of his urine in a cylinder which is labeled "No. 2."

The prostate and vesicles are gently and thoroughly massaged and the patient passes the remainder of the urine into another cylinder, "Specimen No. 3."

We now have three specimens for comparison.

Specimen No. 1 represents the washings from the anterior urethra.

Specimen No. 2 is the bladder urine plus the contents of the posterior urethra.

Specimen No. 3 is bladder urine plus massage products from the prostate and seminal vesicles.

Significance of Urinary Shreds.—In acute urethral inflammation when pus is produced in large quantities the urine is turbid, and contains no shreds. As the inflammation subsides and tends to become localized, an exudate forms over the involved areas but not in sufficient amount to appear at the meatus as a discharge. When washed away by the urine it appears as shreds. These consist of mucus, pus and epithelium and may or may not contain bacteria.

When shreds sink rapidly to the bottom of the cylinder they consist mostly of pus. Lighter shreds which float about and sink slowly consist mostly of mucus or epithelium. In cases treated for a long time with some of the organic silver salts, notably protargol, characteristic heavy, thick, granular shreds, yellow in color, are found. They may appear in the course of treatment after the urine has been clear. Their presence does not indicate that the case is relapsing. Stopping the injections causes their disappearance from the urine in two or three days.

The older writers laid stress upon the size and shape of urethral shreds as indicating the part of the urethra from which they were derived. Experience has shown this view to be incorrect. There is one exception, however. In chronic inflammations of the deep urethra and prostate, a small, fine, light shred is seen, having the shape of a "comma." When this type of shred is found in either the *first* or *second* urines, it invariably indicates a chronic inflammatory process in the prostatic urethra.

Generally speaking, the following conclusion may be drawn:

(1) Shreds do not necessarily indicate gonorrhea. They are frequently found in the urine of men who never had gonorrhea.

(2) Shreds mean localized areas of urethral inflammation.

(3) With the exception of the comma shred, the size and shape of shreds do not indicate what part of the urethra they come from.

Urethral Examination (*The Patient Lying on the Table.*)—The urethra is first palpated by holding the penis in one hand and palpating the outside of the canal with the thumb and forefinger of the other. In this way follicular induration, periurethral abscess, scar tissue or a foreign body in the canal may be detected.

The canal is then examined for infiltrates and stricture. *No instrument should be passed when the urethra is acutely inflamed.* Examinations should be deferred until the local symptoms have subsided. This applies, especially, to *primary acute gonorrheal urethritis and also to acute exacerbations of chronic urethritis.* In chronic relapsing cases when there is much pus, even when it is definitely known that stricture is present, this part of the examination should always be deferred until all acute symptoms have been cleared up. If this rule is adhered to, the management of this especially difficult group of cases will be remarkably free from troublesome complications.

EXAMINATION FOR STRICTURE.—The meatus is first sponged with some antiseptic solution (bichlorid 1-2000, hydrargoxycyanid 1-1000). A metallic bougie-à-boule is dipped into sterile glycerin and inserted through the meatus into the urethra, down to the "cut off" muscle. We generally begin with a No. 25 French bougie. If it enters easily, we go up the scale until we find the largest that the meatus will admit. In case 25 French does not enter, we take up the smaller ones until we find one that will pass through easily. The size of the meatus and the location and size of any narrowings are noted. Local points of tenderness encountered during the passage of the instrument are also registered. A sound corresponding in size to the largest bougie-à-boule is then passed through the urethra into the bladder, and the degree of tenderness of the deep urethra noted.

URETHROSCOPY.—Urethroscopy has for its object the visual inspection of the urethra. It should never be employed in the diagnosis of acute gonorrheal infection or in any condition in which the urethra is acutely inflamed. Urethroscopic examinations should always be employed to complete the diagnosis in chronic urethral inflammation. If carefully and gently performed, we have never seen any evil effects follow. Although in the great majority of cases, very little is learned by this form of examination, valuable information is obtained often enough, at least, to make it a part of the routine examination of all chronic cases.

Various types of urethroscopes are employed. For diagnosis, the direct view irrigation urethroscope, designed by Geiringer (Fig. 1), is employed. Before examining a patient the surgeon should familiarize himself with the various parts of the instrument and their assemblage.

The patient is placed in the endoscopic position with the pelvis near the edge of the table. The urethra is anesthetized if sensitive. The examiner stands at the foot of the table facing the patient. The instrument is dipped into glycerin and gently inserted through the meatus, and passed through the urethra into the bladder. The water and current are then turned on and the examiner, seated on a stool, applies his eye to the telescope. By pulling the instrument forward, a series of images of the bladder and urethra are seen.

Having become familiar with the appearance and landmarks of the normal urethra, we will briefly study the various pathological lesions which can be seen by urethroscopy, as follows:

(1) Chronic urethritis, including stricture; (2) ulcer; (3) polypi; (4) papillomata; (5) calculi; (6) foreign bodies; (7) cysts; (8) chancre and chancroid; (9) prostatism.

(1) *Chronic Urethritis.*—In describing the appearance of the urethra in chronic urethritis we will use the classification of Oberlaender, who divided it into two stages: *first*, the stage of *soft infiltration*, consisting of a small round-cell infiltration of the submucosa; *second*, the stage of *hard infiltration*, which includes all the inflammatory changes by which the round-cell infiltration is changed into connective tissue, the final conversion resulting in stricture. This fibroid change, likewise

affects the urethral glands and crypts. In the early stage of hard infiltration, these are inflamed and either remain open or are plugged with secretion; this, Oberlaender calls the "*glandular form*." Later on, as a result of compression by scar tissue around the glands and crypts, their ducts are closed and the glands are obliterated or converted into small oval or round cysts lying beneath the epithelium. This he calls the follicular or "*dry form*." Small irregular white or yellow patches of sclerotic scar tissue are often seen.

Chronic Posterior Urethritis.—(i) *Soft Infiltration.*—Mucous Membrane.—Dark red or bluish-red areas, slightly elevated, on the mucous membrane, denote the site of infiltrates.

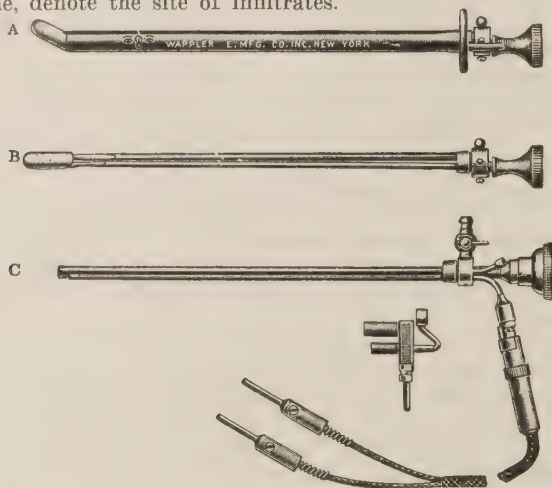


FIG. 1.—DIRECT-VIEW IRRIGATING URETHROSCOPE OF AUTHOR FOR DIAGNOSIS AND TREATMENT

- A. Sheath with movable-beak obturator.
- B. Movable-beak obturator.
- C. Telescope, irrigating faucet, light carrier, channel for probes, filiforms, catheter or fulgurating wire.
- D. Accessory light for local applications.

Glands.—A few may occasionally be seen on the roof. The edges of ducts are thickened and surrounded by a red areola. No glandular openings are visible on the floor of the prostatic sinuses, on account of the redness and swelling of the mucous membrane.

Verumontanum.—This is dark red, swollen, and may fill the entire urethra; the surface is smooth, granular, eroded or lumpy, and bleeds easily.

(ii) *Hard Infiltration.*—(a) *Glandular Form.*—The mucous membrane is pale red, grayish-white or yellow.

Glands.—The mouths of the glands are gaping or plugged with secretion. The edges are swollen and are red or grayish in color.

Verumontanum.—If involved, this may show pale yellow areas; the shape is flattened or distorted.

(b) *Dry or Follicular Form*.—Mucous Membrane.—These are yellowish-white with pale, smooth, sclerotic areas.

Glands.—The ducts are rarely seen. One may see depressed scars, or occasionally, cystic formations (elevated yellowish or grayish-white bodies). In one case of urethritis cystica chronica, the side walls of the urethra were studded with innumerable small cysts. Occasionally single larger cysts are seen having an opalescent milky appearance.

Chronic Anterior Urethritis.—(i) *Soft Infiltration*.—Mucous Membrane.—There are hyperemic areas surrounded by healthy mucous membrane. Erosions are sometimes seen. Granular patches are found on the floor of the bulbous urethra. Thickening is shown by large puffy folds projecting upward into the field. The lumen is gaping or closed, having an irregular crescentic appearance.

Glands.—The crypts and glandular openings are not seen if embedded in the hyperemic areas. Those in the paler areas appear as red elevations discharging pus.

(ii) *Hard Infiltration*.—(a) *Glandular Form*.—Mucous Membrane.—The mucous membrane is paler in color; the surface appears uneven.

Glands.—The glands of Littre are surrounded by a red areola. The openings are enlarged, crater-like or plugged with secretion. The crypts of Morgagni are swollen and gaping, discharging a mucopurulent secretion.

(b) *Dry or Follicular Form*.—Mucous Membrane.—Diseased areas of the mucous membrane are grayish or yellowish white.

Glands.—Very few glands are seen. This is very characteristic of the dry stage, the glands and crypts being obliterated or converted into subepithelial cysts. Very frequently, both glandular and dry forms are seen in the same urethra. This Oberlaender calls "mixed infiltration."

Subacute Anterior Urethritis.—The mucous membrane is red and velvety. The vascular streaks are lost. The mucosa is thrown into thickened folds. The openings of the glands and crypts are red, swollen, and exude pus.

Subacute Posterior Urethritis.—The mucous membrane is dark, red and swollen and sometimes eroded. Occasionally follicular abscesses are seen as small yellowish elevations. The verumontanum is red and swollen.

(2) *Ulcers*.—Ulcers are usually of traumatic origin, resulting from instrumentation. They may, however, be tuberculous. They are most frequently found in the floor of the bulbous urethra. Their borders are irregular with red or grayish necrotic bases.

(3) *Polypi*.—Polypi are seen most frequently in the anterior urethra. They appear as smooth, oval, pedunculated bodies, varying from pale pink to dark red in color.

(4) *Papillomata*.—Two varieties of papillomata are seen in the urethra: (1) *flagellated*; (2) *flat sessile*. The first variety is found most frequently in the deep urethra on or near the sphincteric margin,

or springing from the colliculus. The sessile tumors have a raspberry appearance. They occur most frequently in the anterior urethra just within the meatus. In one case of chronic urethritis complicated by a congenitally contracted hypospadiac meatus, the first half inch of the urethra was almost occluded by these growths.

(5) *Calculi*.—Calculi found lying in the urethra are nearly always of renal origin. Having been passed into the bladder and, after a varying period, having entered the urethra, they are passed through it or caught at some narrow point of the canal. They are found most frequently in the prostatic or bulbous urethra or in the fossa navicularis when the meatus is small. In Guiteras' case, there were four stones found in the pendulous urethra. O'Crowley has reported one in which the bulbous and prostatic portions of the urethra were distended with calculi.

Calculi sometimes originate in the parenchyma of the prostate; these gradually enlarge and, if near the urethral mucosa, break through and are either passed or are caught and require removal. Sometimes the prostatic stone is quite large and remains firmly imbedded in the prostatic tissue and, gradually increasing in size, may break through the urethra; further deposition of salts causes the urethral portion to enlarge, the stone then having an hour-glass or dumb-bell shape.

(6) *Foreign bodies* are rarely found in the male urethra. Bits of catheter, pencils, and pen holders have, however, been reported.

(7) *Solitary cysts* of non-infectious origin are seen but rarely. They have been seen in the deep urethra near the sphincteric margin.

(8) *Chancre and chancroid* of the urethra occur most frequently just within the meatus and can usually be seen without the aid of the urethroscope.

(9) *Prostatic Hypertrophy*.—That portion of the posterior urethra, lying between the verumontanum and vesical sphincter, normally has a cylindrical appearance. In beginning hypertrophy, its transverse diameter becomes narrowed, due to the projection of the enlarged lateral lobes of the prostate into the urethra. In advanced hypertrophy, this narrowing becomes more marked, giving the urethra the appearance of a vertical slit, slightly wider near the urethral floor. The internal vesical sphincter, instead of being round, assumes the same shape.

TREATMENT OF ACUTE GONOCOCCAL URETHRITIS

The treatment of gonococcal urethritis is systemic and local. The former comprises dietetic and hygienic measures, and also the internal administration of curative remedies. The latter deals with the local applications of drugs to the affected parts.

Before taking up the detailed study or consideration of the treatment of gonorrheal infections we will describe the various internal remedies and the drugs employed locally.

I. *Internal Remedies*.—The number of drugs employed in the internal treatment of gonorrhea is legion. This method of treatment is still

the favorite among the laity and the inexpert, because of its comparative harmlessness, ease of administration and the good results apparently obtained in some cases. Careful clinical study and bacteriological control of the progress of cases have very definitely shown that it is unwise to depend on drugs taken internally to effect a cure. Some of them, however, notably the **balsamics**, have a beneficial effect on some of the symptoms of gonorrheal urethritis, and there is no reason why they should not be used, so long as it is borne in mind by the doctor and patient that they play only a secondary part in the local treatment, which is the only method by which the inflammation can be controlled and the gonococcus exterminated.

The internal remedies which enjoy most favor at present are **sandalwood oil**, **copaiba**, **cubebs**, **kava-kava**, **buchu**, **methylene blue** and the **urinary antiseptics**.

Sandalwood oil (*oleum santalis*) is a pale yellow oil distilled from the wood of East Indian *Santalum album*. The dose is 10 to 30 minims (0.6 to 2.0 c.c.) three times a day, three hours after eating, in capsules or emulsion. In some patients, even a small dose of sandalwood oil is irritating to the digestive tract, or it may cause distressing pain in the back, which calls for a diminution in dose or a change of the drug.

Copaiba is a fluid oleoresin obtained from the trunk of a certain species of *Copaifera*. The dose is $\frac{1}{2}$ to 1 dram (2.0 to 4.0 c.c.) in capsules or emulsion. In larger doses or after continued use it is apt to produce indigestion and diarrhea. It occasionally produces an erythema or urticarial eruption.

Cubeb is the dried unripe fruit of *Piper cubeba*. It is less unpleasant to the palate than copaiba and less liable to upset the digestion. In large doses it sometimes irritates the bladder. It is frequently prescribed with copaiba either in pill or emulsion. The dose of the powder is 30 to 60 grains (1.95 to 3.90 grams), fluid extract $\frac{1}{2}$ to 1 dram (2.0 to 4.0 c.c.), oleoresin in capsules, 0.3 to 1 c.c. (5 to 15 minims).

Kava-kava is the dried rhizome of *Piper methysticum* (Polynesia). The dose of the fluid extract is 30 to 60 minims (1.9 to 3.8 c.c.). Its action is similar to the other balsamics, but it has in addition an anesthetic effect on inflamed mucous membranes.

Wintergreen oil is of service when the balsamics disagree. The dose is ten minims in capsule, three times a day.

Methylene blue is seldom employed.

Urinary antiseptics, such as **hexamethylenetetramin**, **salol**, **benzoates** or **benzoic acid**, **boric acid**, **borates** and **methylene blue**, have no appreciable therapeutic effect upon urethral inflammation. These substances, which are of such great value in all urinary suppurative conditions located in the upper urinary tract, are useless below that point. They are useful to protect the kidneys and should be given whenever an unusual rise in temperature occurs during the course of a gonorrhea. Hexamethylenetetramin, commonly known as **urotropin**, is the drug of choice. Its antiseptic action depends upon its power of liberating formaldehyd in the urine. It acts only in acid urine and

should never be prescribed with alkalies. The urine must be tested in every case and if found to be neutral or alkaline, an attempt should be made to alter its reaction by administering **sodium benzoate** 15 to 20 grains (1.0 to 1.3 grams), or the **acid phosphate of sodium** 30 to 60 grains (1.9 to 3.8 grams), twice daily.

The following combinations have been employed in the routine treatment of urethral inflammation:

(1) *Oleum Santali Emulsion.*

R

Olei santali.....	f ʒi (30.0 c.c.)
Potassii citratis	ʒi (31.1 grams)
Syrupi simplicis. }	
Mucil. acaciæ	āā q.s.
Aquæ gaultheriæ }	ad ʒiv (120.0 c.c.)

M. Ft. Emuls.

Sig.: ʒi t.i.d. 2 h. p. c.

(2) *Lafayette Mixture.*

R

Copaibæ.....	
Spiritus etheris nitrosi.....	āā ʒss (15.0 c.c.)
Spiritus lavandulæ.....	
Liquoris potassii (U. S. P.).....	ʒi (4.0 c.c.)
Syrupi simplicis.....	
Mucilagis acaciæ.....	āā q.s.
Aquæ gaultheriæ.....	ad ʒiv (120.0 c.c.)

M. Sig.: ʒii t.i.d. p.c.

Of the foregoing combinations, the writers prefer **sandalwood oil**, either alone in capsules, \mathfrak{m} x four times a day, or combined with **citrate of potash** in emulsion. A very good preparation of the oil in combination with **kava-kava** is prepared under the proprietary name of **Gonosan**. The dose is 6 to 8 capsules during the day.

II. **Local Treatment of Urethritis.**—Before considering the detailed treatment of acute and chronic urethritis, the physician should familiarize himself with the drugs employed and the various methods of applying them to the urethra.

DRUGS.—The list of drugs which have been used in the local treatment of gonorrheal urethritis is a long one. The following table includes only those in general use and many old-time favorites are excluded. New preparations are being constantly proposed, which proves that perfection in urethral medication has not yet been attained.

The following list represents the solutions usually employed, the form in which they are most conveniently kept, and the strengths in which they are employed either for hand injection by the patient, irrigation or instillation.

Name	Form	Hand Injection	Irrigation	Instillation
Silver nitrate.....	50 per cent. solution		1:6000-1:1000	0.5-5 per cent.
Protargol.....	5 grain powders	0.25-1 per cent.	0.1-0.5 per cent.	1-5 per cent.
Argyrol.....	Crystals	5-20 per cent.		10-25 per cent.
Albargia.....	0.2 gram tablets	0.1-1 per cent.	0.05-0.02 per cent.	1-5 per cent.
Novargon.....	Crystals	1:500-1:50	1:3000-1:1000	1:20-1:10
Potassium permanganate.	1 grain tablets		0.01-0.05 per cent.	
Hydrargyrum oxycyanid..	0.25 gram powders		0.01-0.05 per cent.	
Copper sulphate.....	10 per cent. solution		1:500-1:250	
Zinc sulphate.....	5 per cent. solution	0.25-0.5 per cent.	0.1-0.5 per cent.	
Zinc sulphocarbonate.....	Powder	1:500-1:200		
Zinc acetate.....	See text	1:500-1:100		
Vegetable astringents....	See text			
Ointments and bougies...	See text			

The drugs in the foregoing table may be roughly divided into **antiseptics**, **astringents**, **sedatives** and **stimulants**. Most of them exhibit two or more of these functions, either of which will dominate according to the concentration employed. Thus the organic silver salts are essentially antiseptics. **Argyrol** in strengths up to 15 per cent. is sedative, while stronger solutions (25-50 per cent.) are antiseptic, stimulating and also astringent. **Protargol** is antiseptic and astringent. **Silver nitrate** in weak solutions (1-4000) is antiseptic, astringent and mildly stimulating; in 1 per cent. strength, its chief action is astringent, while higher concentrations have caustic properties. **Zinc sulphate** and **acetate** are used only for their astringent properties.

Vegetable astringents, notably **hydrastis**, formerly enjoyed much favor. If used at all, they should only be employed as injections in non-gonorrheal urethritis as substitutes for the zinc salts. Personally, we find them of little or no value.

The application of **ointments**, **oily preparations** and **soluble bougies** containing one or more antiseptic or astringent drugs, still appeals to some. The authors prefer the injection of watery solutions.

The physician should select a few of these drugs and learn thoroughly their dosage, action and mode of administration. It is better to have a complete working knowledge of a few preparations than a hazy appreciation of a large number.

Of the many new preparations for the local treatment of gonorrhea which have appeared in recent years, only two have proven themselves worthy. These are **mercurochrome** and **acriflavine**.

Mercurochrome—220 contains 23-24 per cent. mercury in molecular combination with the dye eosin. In this form the mercury, while retaining its germicidal power, is not precipitated by proteins or alkalis. Young recommends its use as follows:

In Anterior Urethritis.—Solutions ranging from one quarter to one per cent. are injected every three or four hours, the weaker solutions being used in the hyperacute cases. A preliminary irrigation of the anterior urethra with sterile water or normal saline is essential.

In Posterior Urethritis.—First irrigate with sterile water or normal saline to remove mucus and pus. Inject one half to one ounce of a one per cent. solution of mercurochrome by means of a posterior urethral syringe or catheter.

In Female Gonorrhea.—Hager and von Jaekum of the Mayo Clinic recommend the use of mercurochrome, alternating with silver compounds and iodine. During the acute stage, they swab the cervix and vault with tincture of iodine or a 2 per cent. solution of silver nitrate. This produces a profuse desquamation and discharge. The vagina is then wiped dry, and pure crystals of mercurochrome are placed in the cervix. The vault is swabbed out with one per cent. mercurochrome.

In Vulvovaginitis a one per cent. mercurochrome ointment is daily injected into the vagina.

In Ophthalmia Neonatorum Clapp and Martin employ frequent instillations of a two per cent. solution in the eye.

Acriflavine is an antiseptic dye. For urethral injections the strength of the solution used is from 1-5000 to 1-3000. The injections are given three times a day, holding in the fluid for five minutes.

COMPARATIVE VALUE OF LOCAL REMEDIES.—Just as in other obstinate conditions, there is a diversity of opinion regarding the relative merits of the various local remedies employed. Differences of opinion exist among urologists as to the relative values of the organic silver salts. This confusion is added to by the manufacturers, each of whom extols the value of his own preparation.

Much work has been done in the laboratory and upon animals to test the value of various drugs. Thus Marshall and Neave found that, whereas the majority of silver salts were powerfully bactericidal upon the *Staphylococcus pyogenes aureus*, argyrol showed no such effect.

According to Cragin, argyrol in 20 per cent. strength destroys the gonococcus in 20 seconds, but is inefficient with streptococci and *Staphylococcus pyogenes aureus*. Burnett, in his experiments, showed that neither argyrol nor silver nitrate showed any power to penetrate the urethral mucous membrane.

From the foregoing, the impracticability of classifying these salts by laboratory or test-tube standards becomes evident. Clinical experience is the only criterion, and it has shown that the **organic silver salts** are the best remedies in acute gonococcal inflammations, by virtue of their being bactericidal and relatively non-irritating. In chronic gonorrhea they are useful only when the urethra is very sensitive and irritable to silver nitrate, which is the remedy of choice.

Personally, we find **argyrol**, **protargol** and **silver nitrate** the most efficient in the routine treatment of acute and chronic urethritis. We have practically discarded the use of **potassium permanganate**, finding it inferior to either protargol or argyrol. Although it apparently seems to hasten the cure by diminishing the discharge more quickly than the silver salts, it gives the physician and patient a sense of false security as to the progress of the case. Discontinuing the injections frequently causes the prompt reappearance of the discharge, very often to the bewilderment of the physician and the discouragement of the patient.

THERAPEUTIC VALUE OF MERCUROCHROME AND ACRIFLAVINE.—Clinical experience has shown that these drugs are valuable adjuvants in the treatment of gonorrhea. In our experience they rank about the same as protargol and argyrol. The practitioner must not, however, rely solely upon either of them in treating all cases, otherwise he will meet with

many failures. Best results are obtained when they are employed alternately with the silver salts. Used in this way, there is no danger of the gonococcus developing a tolerance for or a resistance to any particular drug.

Mereurochrome is objectionable for home treatment because of its intense staining qualities. For this reason we use it only in the office. When we first started to use it, we found that it proved very irritating when instilled into the deep urethra. In fact several cases developed acute prostatitis and epididymitis which we attributed to the irritating effects of the drug. At present, if we decide to employ it at all in posterior gonorrhea we first administer a course of the milder silver salts, in order to determine the tolerance of the deep urethra to treatment. In the treatment of periurethral abscess and sinuses mereurochrome is more effective than acriflavine and the silver salts.

Astringent injections of zinc and alum are of no value in gonococcal urethritis. They are but little used except in controlling the discharge in chronic anterior urethritis until more efficacious local treatments effect a cure.

METHODS OF ADMINISTRATION.—The application of remedial agents to the urethra is performed in the following ways: (1) Injection with a small syringe. (2) Irrigation with (a) large piston syringe, (b) irrigating jar. (3) Instillation. (4) Urethroscopic application.

The patient should empty his bladder immediately before any treatment is applied to the urethra, thereby washing out any discharge which may be present and also enabling the surgeon to note the progress of the case by the appearance of the urine.

(1) *Injection with a Small Syringe.*—These are generally applied by the patient himself. He is instructed to provide himself with a two-dram glass or hard rubber syringe having a *blunt tip*. The tip may also be of soft rubber. The syringe is filled and applied snugly within the meatus, aided by lateral pressure applied with the thumb and forefinger of the left hand. The injection is made slowly and there is no need for the patient to press against the urethra to prevent the solution from entering the bulbous urethra.

In acute gonorrhea, the injection is made three or four times a day. In chronic gonorrhea, not oftener than twice a day. The solutions usually employed are: protargol $\frac{1}{4}$ to $\frac{1}{2}$ per cent., argyrol 10 to 20 per cent.

(2) *Irrigation.*—This is accomplished either with a large piston syringe of the Janet-Frank type (Fig. 2), or with an irrigating jar suspended from the wall. The nozzle of the syringe should be blunt-tipped. This method has for its object the flushing out of the anterior and also of the posterior urethra. The nozzle is pressed against the meatus and enough fluid injected to distend the urethra, after which the fluid is allowed to flow out. This intermittent irrigation is continued until the syringe is emptied. In order to irrigate the deep urethra and bladder, the nozzle is held firmly against the meatus and the fluid slowly injected. To relax the sphincter muscle, the patient is instructed to breathe deeply or to attempt to urinate. Usually, after a few minutes, the "cut-off" muscle relaxes and the solution flows through the deep

urethra into the bladder. When enough of the solution has been passed the patient empties his bladder, thus securing a two-way irrigation.

The authors find this method a cumbersome one and very tiring if many patients are to be treated. The irrigating jar will be found



FIG. 2.—JANET-FRANK SYRINGE.
(Kny-Scheerer.)



FIG. 3.—CHETWOOD'S IRRIGATING NOZZLE.
(Kny-Scheerer.)



FIG. 4.—KIEFER'S IRRIGATING NOZZLE.
(Kny-Scheerer.)

much more convenient. The apparatus consists of a one-quart jar suspended from the wall about 3 to 5 feet above the level of the table. About 5 feet of rubber tubing is attached to the jar.

Various nozzles are employed (Figs. 3 and 4). The Chetwood scissors and two-ways glass nozzle for irrigating the anterior urethra, the Swinbourne cut-off and shield and the Janet nozzles are recommended.

The irrigation of the anterior or posterior urethra is performed in the same manner as with the piston syringe.

Instead of employing hydrostatic pressure to relax the cut-off muscle when the deep urethra and bladder are irrigated, catheter irrigation may be used. The technic is as follows: A straight soft rubber 12-14 Fr. catheter is lubricated either with glycerin or other lubricating jelly. The catheter is then introduced into the bladder. The irrigating jar is connected with the catheter by means of a fine-pointed nozzle. About two ounces of the solution are allowed to flow into the bladder. The catheter is then disconnected from the jar, and as the solution

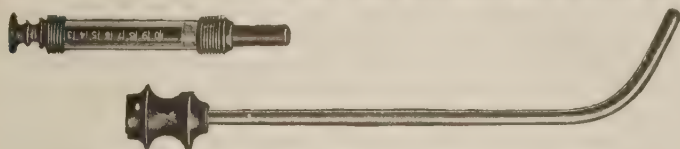


FIG. 5.—ULTZMANN'S INSTILLATION SYRINGE. (Kny-Scheerer.)

flows out of the bladder, through the catheter, the latter is gently withdrawn about 3 to 4 cm. until the flow stops, which shows that the eye of the catheter lies within the prostatic urethra. The catheter is again connected with the irrigating jar, and the solution flows into the catheter, through the prostatic urethra into the bladder. When the patient feels a desire to urinate, the flow is stopped and the catheter withdrawn. The patient gets off the table and empties his bladder.

The authors prefer the irrigation of the deep urethra with a catheter. It is much more convenient and less trying to the patient, unless he can easily voluntarily relax the sphincter muscles. In nervous patients, it



FIG. 6.—GUYON INSTILLATION SYRINGE. (Kny-Scheerer.)

is sometimes at first impossible to pass a soft catheter into the bladder, owing to spasm of the "cut-off" muscle, in which case a woven coude catheter should be used.

(3) *Instillations*.—The object of instillation is to place upon a given portion of the urethra a few drops of a concentrated solution. The instillator (Figs. 5 and 6) consists of a syringe barrel to which is attached a hollow metal catheter, as in the Ultzmann or Keyes instrument, or a woven catheter of the Guyon type. The authors prefer the Ultzmann instillator. The metal catheter portion of the instrument is made either of steel or silver. The former, owing to oxidation, becomes clogged up, whereas the silver catheter always remains patent.

Inasmuch as instillations are nearly always made in the deep urethra, the surgeon should have a clear idea of the precise position of the in-

strument when it passes the external sphincter. Usually, a distinct "jump" is felt as it passes over the "cut-off" muscle. In case of doubt we may always feel certain that the point of the instrument is in the deep urethra when its shaft rests without support at an angle of 45 degrees to the horizon.

(4) *Urethroscopic Applications*.—These are considered under chronic urethritis.

III. Routine Treatment of Acute Gonorrheal Urethritis.—**ACUTE ANTERIOR URETHRITIS.**—The intensity of the inflammation may vary within wide limits. In some, which for convenience may be termed *hyperacute*, the local reaction is very intense, characterized by marked swelling and eversion of the meatus, swelling and redness of the glans and prepuce, profuse greenish-yellow purulent discharge, which may be blood streaked, and intense burning on urination. In others, which may be called moderately severe or *acute* cases, the local signs are much less marked. It is important to consider the intensity of the inflammation when beginning the treatment, because if injections are started too soon in the hyperacute type, the symptoms are aggravated, frequently causing an extension into the deep urethra and prostate.

When a patient with acute urethritis presents himself for treatment, he is examined as previously described. When the diagnosis of acute anterior gonorrhea has been made, the patient is given instructions regarding cleanliness, diet, rest and sexual hygiene.

Cleanliness.—The parts should be washed as often as necessary with soap and water. The discharge should be collected in a small gauze bag which is tied around the waist and in which the penis is placed. A number of these are on the market. If the prepuce is long, the glans penis may be thrust through a slit in the center of a square piece of gauze, over which the foreskin is then drawn.

The patient is advised to wear a jock strap as a preventive of epididymitis. This, incidentally, serves to hold the cotton or gauze covering the glans. Packing the prepuce with gauze is a bad practice because it prevents proper drainage. The patient is warned of the danger to his eyes from contamination with gonorrheal pus. He is told to thoroughly wash his hands with soap and water every time he touches his penis.

Diet.—Meat in excess, highly seasoned or salty foods, sauces, condiments, strong tea or coffee, pickles, tomatoes and asparagus, should be avoided. Alcohol, ale, beer, cider and ginger ale are not allowed. Keyes' rule, that any substance which burns the palate as it enters the body will burn the urethra as it issues forth (chemical not physical heat is meant), is a good one.

Water.—About eight glasses of water should be drunk during the day. Sparkling water or French Vichy may be used.

Rest.—Patients are instructed to take as much rest as possible. It is better to ride than to walk and to sit rather than to stand. The shaking and jolting in railway trains and automobiles seems particularly injurious.

Sexual Hygiene.—Sexual intercourse must not be indulged in until

the disease is cured. Anything liable to induce sexual excitement, such as association with women, suggestive literature and pictures, should be avoided, otherwise the resulting congestion of the deep urethra and prostate favors the extension of the inflammation into these organs.

Internal Medication.—The **sandalwood oil emulsion** (*see* p. 478) is given as long as there is a free urethral discharge. When the discharge is scanty and has changed from frank pus to a thin grayish mucus, there is nothing to be gained by giving the balsamics or, in fact, any other urinary antiseptics. The best guide is the appearance of the urine. So long as the urine is turbid (due to pus) sandalwood oil alone or in combination is kept up, provided it does not upset the digestion too much. If the patient objects to the taste of the emulsion, which is very disagreeable, sandalwood oil may be given in 10 minim capsules, one capsule three times a day after meals and on retiring. The authors prefer **gonosan** capsules; dosage, two capsules four times a day. Some patients tolerate the oil better on an empty stomach. Others do better when it is taken one hour after meals.

In moderately severe cases, the patient can at once be placed on a hand injection of $\frac{1}{4}$ per cent. **protargol**. The injection is made four times a day and retained for five minutes each time. Soaking the penis in hot water seems to intensify the action of the injection and to moderate the pain. Ten per cent. **argyrol** may be used instead. This is so messy, owing to its deep color, that protargol is preferable. As a rule, the pain caused by protargol in this strength lasts but a few moments and is readily borne. After three or four days, the strength of the injections can safely be raised to $\frac{1}{2}$ per cent. If it produces severe or lasting pain it should be reduced to the former strength. Some urologists employ protargol up to 2 per cent. Our own experience has taught us that nothing is gained by these higher concentrations in acute urethritis. One per cent. may be employed. Usually, however, it causes irritation.

In hyperacute cases, injections are not begun until the local symptoms subside. This may be hastened by prolonged soaking of the penis in hot water. When the authors consider that the case is ready for local treatment, they inject one dram of 15 per cent. argyrol into the anterior urethra. This is retained for five minutes. This is repeated on the following day and if no irritation is produced the patient is instructed how to inject himself with the protargol solution. *The silver salts are employed as long as gonococci are present in the discharge or urine.*

When the gonococci can no longer be demonstrated, it is still the custom of many to employ an **astringent injection** of the following type:

R		
Aluminis	}	
Zinci sulphatis		
Phenol		
Glycerini		℥ss (15.0 c.c.)
Aquæ destillatæ		ad ℥iv (120.0 c.c.)
M. Sig.: Inject b.i.d.		

The authors do not employ them, however, relying upon the astringent properties of **silver nitrate**.

Office Treatment.—The duration of the disease may be shortened by treatment in the office. Flushing the urethra with **warm protargol solution** $\frac{1}{8}$ to $\frac{1}{4}$ per cent., temperature 100° - 105° F. (37.8° - 40.6° C.), materially hastens the disappearance of the discharge. This is performed once a day, until the discharge shows signs of letting up, when every other day will be sufficient.

Protargol irrigations are kept up as long as the urine is cloudy, due to pus.

When the urine is almost clear and contains shreds, then **silver nitrate** is the drug of choice. In weak solutions, its action is antiseptic and astringent.

We begin with a 1-8000 solution, and gradually increase in strength, rarely exceeding 1-1000. The **irrigations** are preferably made with an irrigating jar suspended about three feet above the level of the table. Irrigations are given on alternate days. **Distilled water** is preferable to tap water. The temperature of the water should be from 100° - 105° F. The authors employ a stock solution of silver nitrate 100 per cent. strength for making dilutions. Two drops of this solution added to 1 quart of water make approximately 1-8000 dilution.

The following table for increasing the strengths of silver nitrate solutions in both acute and chronic urethritis will be found useful:

1st day,	2 drops	100 per cent.	AgNO ₃	Solution = 1-8000	approximately
3d "	3 "	" "	" "	" "	= 1-6000 "
5th "	4 "	" "	" "	" "	= 1-4000 "
7th "	5 "	" "	" "	" "	= 1-3200 "
9th "	6 "	" "	" "	" "	= 1-2800 "
11th "	7 "	" "	" "	" "	= 1-2300 "
13th "	8 "	" "	" "	" "	= 1-2000, etc.

From the foregoing table it will be seen that the strength of the solution is increased one grain to the quart each time.

If at any time the silver nitrate causes irritation, evidenced by increased pain following administration, weaker dilutions must be used. *If used with judgment and proper strengths in the subsiding stages of the inflammation, better results will be obtained with silver nitrate irrigations than with any other preparation. If on the other hand it is employed in the acute stage or in strong solutions, only harm will result. Furthermore, the patient should never be allowed to use the nitrate for hand injections.*

Frequently when employed in concentrations over 1-2000, a discharge may appear within a few hours, or the patient may notice it the following morning. Unless the solution is too strong, this discharge usually disappears promptly in the first twelve hours following irrigation and is of no significance. *In all events, the irrigation must not be repeated until all signs of local reaction have disappeared.*

During the course of the disease certain symptoms call for special attention, such as:

Chordee.—This distressing symptom can often be prevented by **prolonged soaking of the penis in hot water** before retiring and the internal administration of the following:

R
Sodii bromidi $\mathfrak{z}\text{i}$ (31.1 grams)
Hyoseyaminæ hydrobromidi grain $\frac{1}{4}$ (0.016 gram)
Aquæ menthæ piperitæ..... ad $\mathfrak{z}\text{iv}$ (120.0 c.c.)

M. Sig.: $\mathfrak{z}\text{i}$ on retiring, to be repeated once during the night.

Lupulin grains xxx-xl (2.0-2.6 grams) at bed time, **monobromid of camphor** grains v (0.3 gram) are sometimes effective. In specially severe cases the following **rectal suppositories** may be used, but with caution:

R
Morphinæ sulphatis grain $\frac{1}{4}$ (0.016 gram)
Quininæ sulphatis grains x (0.65 gram)
Olei theobromatis q.s.

M. Ft. Rectal Suppository.

Sig.: Insert one at bed time.

The patient should be instructed to **lie on his side**. The time-honored method of tying a towel around his waist with the knot in the back may assist him in this.

Ice water is useful when the penis is erect and in *chordee*. The patient usually urinates if he can and then by immersing the penis in cold water, he usually succeeds in reducing the erection. Slowly bending the rigid member downward and retaining it between the thighs often helps.

Severe Burning on Urination.—This symptom rarely calls for special attention in acute anterior urethritis. Diluting the urine by **drinking freely of water** usually moderates it. In severe cases the following mixture is useful:

R
Liquoris potassii (U. S. P.)..... $\mathfrak{z}\text{i}$ (30.0 c.c.)
Tincturæ hyoseyami $\mathfrak{z}\text{i}$ (30.0 c.c.)
Syrupi cinnamomi ad $\mathfrak{z}\text{iv}$ (120.0 c.c.)

M. Sig.: $\mathfrak{z}\text{i}$ in glass of water 2 h. p. c.

Under the foregoing methodic treatment, favorable cases clear up in from six to eight weeks. The reader is referred to p. 512 for the various tests employed to determine whether the patient is cured.

ACUTE POSTERIOR URETHRITIS.—When gonorrheal inflammation involves the deep urethra, there is always some involvement of the prostate gland. The degree of prostatic inflammation may be so slight that there is no apparent change which can be detected, or the entire gland

may be involved. Under this title we will consider the treatment of posterior urethritis unaccompanied by any palpable change in the prostate.

During the treatment of acute anterior urethritis the urine voided in two glasses should be examined at each visit. The appearance of pus in the second glass denotes invasion of the posterior urethra.

Local treatment of the posterior urethra will depend upon:

- (1) Intensity of the inflammation in the anterior urethra.
- (2) Intensity of the inflammation in the deep urethra.

This brings the following types of cases up for consideration:

(1) When the inflammation in the anterior urethra is very severe, no local treatment is applied to the posterior urethritis.

(2) When the anterior urethritis is moderately severe and under control, treatment of the posterior urethra can be begun at once, except in the case mentioned under (3).

(3) When the posterior urethritis is very severe, as shown by subjective symptoms of painful and frequent urination, tenesmus, etc., the physician can begin local treatment at once or wait until the severity of the symptoms subsides.

The type of treatment will depend upon the experience of the physician and the previous history of the patient. If pains and frequency increase or do not diminish under local treatment, it should be discontinued. *When in doubt stop all local treatment.*

Treatment of the posterior involvement is usually begun with **instillation of argyrol** 15 per cent. once or twice a day. If well tolerated 25 per cent. argyrol is used. The patient at the same time keeps up the hand injections for the anterior urethra. The argyrol treatment is kept up until all subjective symptoms disappear and the second urine becomes clear. If the second urine still contains pus, or shreds persist, **catheter irrigations of silver nitrate** beginning with 1:8000 and cautiously increased in strength are employed.

When the anterior inflammation is very acute, all local treatment is stopped. **Sandalwood oil** is administered internally (see anterior urethritis), and the patient is told to rest as much as possible. It not infrequently happens that, in the course of a few days, the second urine will clear up and no treatment of the deep urethra will be necessary. This applies only to the mild posterior involvement. If the subjective symptoms increase, the patient is put to bed, and a **hot-water bag** applied to the perineum. **Hot rectal saline injections** are given twice a day. The following formula will assist in moderating the frequency, burning and tenesmus:

R

Kalii (potassii) acetatis	℥i	(31.1 grams)
Tincturæ belladonnæ	℥ss	(15.00 c.c.)
Aquæ menthæ piperitæ	ad ℥iv	(120.00 c.c.)

M. Sig.: ℥i t.i.d. between meals in a glass of water.

If the pain and frequency continue to increase, **sedative suppositories** of the following type may be employed:

R

Morphinæ sulphatis grain $\frac{1}{4}$ (0.016 gram)
 Quininæ sulphatis grains x (0.65 gram)
 Olei theobromatis q.s.

M. Ft. Rectal suppositories.

To be inserted once or twice a day.

R

Morphinæ sulphatis grain $\frac{1}{4}$ (0.016 gram)
 Antipyrinæ grains x (0.65 gram)
 Olei theobromatis q.s.

M. Ft. Rectal suppositories.

To be inserted once or twice a day. These suppositories should be stopped as soon as the symptoms moderate.

Some urologists recommend in these cases the instillation of 2 or 3 drops of 5 to 10 per cent. **silver nitrate**, claiming that it often causes a marked diminution in pain. Although this procedure is of value in relieving irritability of the deep urethra, due to causes other than gonorrhea, the writers do not recommend it in acute posterior gonorrhea, on account of the possibility of setting up an acute prostatitis or epididymitis. When the symptoms have subsided, treatment of the anterior and deep urethra is continued as described above.

IV. **Prophylaxis**.—To avoid gonorrhea, the man should urinate immediately after coitus and thoroughly **wash with soap and water**. The use of a **condom** is a perfect safeguard against infection unless accidentally ruptured during coitus.

The following therapeutic measures afford a reliable means of preventing infection, if employed within 6 hours after exposure and no later than 12 hours:

(1) **Instillation** in the meatus of **25 per cent. argyrol** freshly prepared.

(2) **Injection** of **3 per cent. protargol**.

(3) **Irrigation** of the anterior urethra with 1:1000 **potassium permanganate**.

(4) *U. S. Navy Prophylaxis*: On his return from shore leave, the sailor washes his genitals with soap and water and urinates. An injection of 1 c.c. of **2 per cent. protargol** containing **15 per cent. glycerin** is retained for five minutes. To prevent syphilis, **calomel ointment** is applied to the external genitals and left on for two hours.

V. **Abortive Treatment**.—The abortive method has for its object the quick cure of a beginning gonorrhea. Many methods of treatment have been advised, some more complicated than others. The originators are very enthusiastic over the results obtained by their respective methods.

Thus Frank and Lewin report 45 per cent. cures; Bierhoff 50 per cent. To insure success treatment must be begun within a few hours after the appearance of the discharge.

It is the experience of most observers that only in exceptional cases is it possible to abort gonorrhea. Most are agreed that, although at times rapid cures are obtained in secondary gonorrhea, it is almost impossible to abort a primary attack. The authors' own experience has led them practically to give up any attempt to abort gonorrhea by any special method. They occasionally obtain quick results with the routine treatment outlined in acute anterior urethritis. At any rate, if failure results from this method, no harm has been done, as is frequently the case when strong injections are made in attempting to abort the disease in a few days.

The drugs employed are **protargol** ranging in strength from 1/6 to 4 per cent., **silver nitrate** 1:3000, **argyrol** 5 to 25 per cent., and **potassium permanganate** 1:5000 to 1:1000.

For the detailed description of the various methods, the reader is referred to the larger special works on this subject.

TREATMENT OF CHRONIC GONORRHEA IN THE MALE

In beginning the treatment, the question of chronicity should, for the time being, be entirely disregarded. The treatment should be palliative, along the lines described under the acute infection. When the acute process subsides, then the case should be examined for chronic foci and the proper treatment for these applied.

When a patient with chronic gonorrhea presents himself for treatment, it is essentially important for the physician to study the extent and nature of the lesions present, before outlining the treatment.

Frequently, the condition of the patient when first seen is very apt to mislead the examiner, unless a careful history is taken, and a thorough routine examination is made as described on page 469.

Chronic cases of urethral or prostatic gonorrhea, when first seen during an acute exacerbation, are especially puzzling. Thus a chronic anterior urethritis may simulate an acute anterior inflammation of recent origin. This, in turn, may invade the deep urethra and prostate, or on the other hand, a chronic prostatic gonorrhea lights up and infects the anterior urethra. In this way, an acute relapse of a chronic gonorrhea may obscure the location of chronic infected areas.

A careful history will usually not only reveal the existence of a previous infection, but also reveal certain symptoms which indicate that the patient had not been cured of previous attacks.

When there is a history of many attacks of urethritis occurring within a short space of time, it is reasonable to assume that these, so-called acute attacks of gonorrhea, are acute relapses of a chronic gonorrhea.

In all chronic cases, the physician should also remember that in the great majority, probably 85 per cent., there is an involvement of the

deep urethra and prostate. Unless these cases are examined from this standpoint, many errors in diagnosis and failures in treatment will result. For therapeutic purposes, chronic gonorrhea may be classified as follows: (1) *chronic anterior gonorrhea*; (2) *chronic posterior gonorrhea*; (3) *chronic anteroposterior gonorrhea*; (4) *acute exacerbations of chronic gonorrhea*.

(1) **Chronic Anterior Gonorrhea.**—When chronic gonorrheal inflammation is present in the anterior urethra, the lesions most frequently responsible for the persistence of the infection are folliculitis and stricture. Fistulae resulting from periurethral abscess may also be the underlying cause.

FOLLICULITIS.—This condition is readily diagnosed with the water dilatation urethroscope. The indications for *treatment* are (1) to cause absorption of the periglandular infiltrate, (2) to destroy the gonococci. The former is accomplished by **dilatation**, the latter by **antiseptics**.

If an active urethral discharge is present the patient employs a hand injection of **protargol** $\frac{1}{2}$ per cent. Twice a day is sufficient. The administration of **internal urinary antiseptics** is of doubtful benefit unless acute inflammation is present, or if the urine is turbid, due to pus.

In quiescent cases, **irrigations** of the anterior urethra are given every second day. **Silver nitrate** is the remedy of choice. Weak dilutions should always be used in the beginning. It is always safe to start with 1-8000. The strength is gradually increased according to the method described on page 486. Usually the irrigations can be given every second day. They must not be repeated until the irritation (increased discharge and burning) produced by the previous treatment has subsided.

Dilatation may be performed with metal sounds or dilators. The authors prefer the dilators (Figs. 7-10). If used with gentleness, less pain is caused and higher degrees of dilatation are obtained. Local anesthesia should never be employed to lessen the pain of dilatation because extreme pain is, in itself, a contraindication to dilatation. It is essential also to have a fair-sized meatus to facilitate instrumentation. If the meatus is less than 25 French, it should be cut to admit a 31 sound.

To determine what size sound to begin with, **olivary bougies** are passed. A sound corresponding in size to the largest bougie which the urethra can readily admit, is lubricated and introduced into the urethra down to the "cut off" muscle. The urethra is then gently massaged over the sound. This assists in expressing little plugs of secretion from the mouths of the inflamed glands. Allowing the sound to remain in the urethra for 10 or 15 minutes, as was formerly the custom, is unnecessary and may cause irritation and spasm. After dilatation, the urethra is **irrigated** with the **silver nitrate solution**. At the next visit a sound one number larger is inserted. If local treatment causes a marked increase in discharge and urethral tenderness and soreness it should be discontinued until all urethral irritation has subsided. When the urethral discharge has stopped and nothing but shreds remain, the hand injection



FIG. 7.—OBERLÄNDER'S ANTEROPOSTERIOR URETHRAL DILATOR. (Kny-Scheerer.)



FIG. 8.—KOLLMANN'S URETHRAL DILATOR, TYPE USED FOR DILATING THE ANTERIOR URETHRA. (Kny-Scheerer.)

is discontinued and the treatment completed with dilatation and irrigations.

Special urethral dilators of the Oberlaender and Kollmann type give better results than the metal sounds, because in many cases of long-standing inflammation, it is necessary to dilate the urethra as high as 35 or 38 French. When dilators are employed, the blades should always be covered with a rubber sheath.

The foregoing treatment usually clears up a case, in from 6 to 12 weeks; occasionally, we meet with cases that clear up to a certain point and then remain stationary despite all efforts. If these are urethroscoped, one occasionally sees scattered here and there throughout the urethra, large gaping glandular openings surrounded by plaques of scar tissue frequently containing purulent plugs. It is our custom to introduce a fulgurating wire through the urethroscope and destroy the gland with the **Oudin spark**. This procedure should only be performed after



FIG. 9.—KOLLMANN'S URETHRAL DILATOR, ANTEROPOSTERIOR DILATING BLADES. (Kny-Scheerer.)

the urethra has received a thorough course of dilatation and irrigation.

URETHRAL FISTULA.—Occasionally a persistent fistula, resulting from periurethral abscess, harbors gonococci, which from time to time cause acute relapses of urethral inflammation.

When permanent fistula results, it should be *treated* by **Chetwood's method**. A few drops of a 25 per cent. **ethereal solution of hydrogen peroxid** are injected, preferably through the urethral end of the fistula, employing a hypodermic needle with a blunt point.



FIG. 10.—KOLLMANN'S URETHRAL DILATOR, BLADES FOR DILATING POSTERIOR URETHRA OR PROSTATE. (Kny-Scheerer.)

If this is not successful, **fulguration** will sometimes obliterate the lumen. The wire is inserted as deeply as possible in the tract, either from the urethral side or, if that be impossible, in the outer opening, and the current turned on until bubbles of gas are seen escaping. In a week this can usually be repeated.

If these methods are not effectual, a **plastic operation** must be done.

STRICTURE.—Urethral stricture resulting from chronic gonorrhea has been variously described as linear, annular, tortuous, irregular, etc.

For prognostic consideration the following points are important:

(i) *Location of the Stricture.*—Strictures located anterior to the penoscrotal junction are less serious and easier to treat than those situated in the bulbous urethra.

(ii) *Caliber of Stricture*.—Infiltrations larger than 25 Fr. are readily dilated and rarely relapse or contract. Infiltrations smaller than 25 Fr. show a tendency to contract after treatment.

(iii) *Is the Stricture Soft or Hard?*—Soft infiltrations are of more recent origin and are readily dilated and rarely relapse. Hard infiltrations mean fixed connective tissue formations, which are difficult and frequently impossible to dilate. They frequently relapse after prolonged dilatation.

(iv) *Is the Stricture Passable or Impassable?*—A patient may have a fair urinary stream in spite of the fact that it is impossible to pass a dilating instrument through the urethra, owing to its irregular and tortuous course. These impassable strictures show a progressive tendency to contract and usually require operative measures for their relief.

(1) *Treatment of Stricture of Large Caliber*.—Infiltrations larger than 15 Fr. come under this heading.

In the passage of **dilating instruments** it should be borne in mind that the brutal passage of a sound, by bruising and tearing the inflamed urethra, sets up a sharp reaction which frequently causes further contraction of the infiltrate by increasing the inflammatory exudate.

The instrument properly sterilized and warmed is introduced into the urethra with the utmost care and gentleness. Its size should correspond to that of the bougie which has been passed through the stricture. When the sound has entered the bladder it is gently withdrawn at once. A second and a third sound may be passed if the first sound has entered easily.

After the passage of sounds, the urethra and bladder are **irrigated** through a soft rubber catheter with 1-8000 **silver nitrate solution**. In addition, the patient is given **hexamethylenamin**, grains x (0.6 gram) before and immediately after instrumentation.

If the treatment is not properly performed, epididymitis, urinary fever, and traumatism to the stricture may result. These complications not only aggravate the patient's condition, but defeat the object of the treatment. They can usually be avoided by the administration of **urotropin** before and after instrumentation, gentleness in the passage of sounds and irrigation of the bladder and urethra immediately following.

The interval between the passage of sounds will depend entirely upon the reaction following. Usually, even after the most gentle instrumentation, a local reaction of more or less intensity appears within 24 hours. The succeeding dilatation should never be performed until the local reaction resulting from the previous treatment has completely subsided. Three days is nearly always a safe interval.

At each subsequent visit, the dilatation is begun with a sound one or two numbers smaller than the last size introduced at the previous visit. The dilatation is then carried on as far as possible without the employment of force.

The "End Point" of Dilatation.—Urologists differ on this point.

Some use the size of the urethral meatus as a gauge, providing it is not congenitally small or contracted by disease. Others disregard the meatus and dilate up to 31 or 32 French.

The following course is recommended: Unless the penis is very small, the urethra is dilated until it will readily admit a 30 French sound. If the meatus is below 25 French, it is cut to 31 French. If larger than 25 French, sounds are passed until the size of the meatus is reached, after which the dilatation is completed with either **Oberlaender** or **Kollmann dilators**.

Irritable and Bleeding Stricture.—Occasionally, even when the utmost gentleness is employed in passing sounds, profuse bleeding follows. When this occurs, dilatation should be postponed, until the congestion has been diminished by a course of irrigations with silver nitrate solutions. In these cases, the use of the Oberlaender dilator instead of sounds is less apt to provoke hemorrhage.

(2) *Stricture of Small Caliber.*—In this class belong strictures of less than 15 French caliber. The dilatation of these tight strictures is best begun with **woven silk bougies**, owing to the danger of making false passages when small metallic instruments are used. When the dilatation with small instruments has been carried up to 15 French, metallic instruments may then be employed.

(3) *Impassable Stricture.*—The urethral infiltrate may be so irregular, nodular and tortuous that neither an olivary bougie or sound can be passed through it. Two types are met with: (1) *uncomplicated impassable stricture*, in which the patient can empty his bladder, although the urinary stream is small; (2) *impassable stricture with retention*. If the patient can void, every effort should be made to pass an instrument into the bladder. Perseverance, gentleness and skill very often succeed.

Technic.—A 4 per cent. **novocain solution** with **adrenalin** (gtts. x: 1 ounce) is injected in the urethra and retained for five minutes. A **filiform** is then introduced into the urethra. If it is caught, others are passed alongside, until the urethra is filled, after which, attempts are made to engage the stricture by manipulating one filiform after the other. If successful in passing a filiform into the bladder, a **tunneled sound** is threaded over the filiform and inserted into the bladder.

If it is impossible to pass a filiform by this method, a **water dilatation urethroscope** (Fig. 1) is introduced into the urethra down to the stricture and its orifice looked for. A filiform then is passed through the urethroscope and an attempt made to guide it through the stricture by direct observation.

Impassable Stricture Complicated by Retention.—When retention occurs, the patient is placed in a **hot bath** for 15 to 20 minutes and should attempt to empty his bladder while in the bath. If he succeeds, an attempt at dilatation should be made, as described in the foregoing section.

If unsuccessful, the bladder should be **aspirated** every eight hours for one day by **suprapubic puncture**. If still unable to void, and an-

other attempt to introduce filiforms is unsuccessful, the stricture is considered impassable.

Indications for Operation.—The types of strictures requiring operation are as follows:

(1) Any stricture that resists dilatation or shows a tendency toward progressive contraction after a course of dilatation.

(2) Impassable stricture, with or without retention.

(3) Resilient stricture.

(4) Tortuous nodular strictures of long standing, and irritable strictures complicated by severe cystitis are best treated by resection or division, especially when located behind the penoscrotal junction.

Type of Operation.—In general, **internal urethrotomy** is performed for strictures located anterior to the penoscrotal junction. If the stricture is of long standing and of small caliber, and complicated by severe cystitis, perineal section is performed, in addition, for drainage.

External urethrotomy is performed for strictures located behind the penoscrotal junction.

When strictures are present in both the pendulous and deep urethra, the **combined operation** is performed.

(2) **Chronic Posterior Gonococcal Infection.**—When gonococcal inflammation invades the deep urethra, there is always some involvement of the prostate. This involvement may be mild or severe. The same holds true for the seminal vesicles; they rarely escape infection when the prostate is affected, owing to their close anatomical relationship.

As a result of chronic inflammation certain changes take place in these structures. The infection first invades the ducts of the prostatic glands and later the glands themselves. At the same time, an inflammatory exudate is deposited in the parenchyma of the glands and also between them in the interstitial tissues. This infiltration causes the mucous membrane of the acini to become swollen. The lumen of the gland ducts becomes narrowed, so that the drainage of inflammatory products produced within the glands themselves is interfered with.

The inflammation frequently extends through the ejaculatory ducts and involves the seminal vesicles. The mucous membrane of the ducts becomes swollen and the lumen narrowed, causing retention of products and suppuration within the vesicles.

The same changes take place in the urethra and verumontanum, so that if the condition is not relieved, the round-cell infiltration becomes organized and sclerosis results. This sclerosis causes either partial or complete obstruction of many of the prostatic glands, resulting finally in obliteration of the ducts with focal suppuration and destruction of the prostatic parenchyma.

As a result of these changes, the deep urethra becomes hypersensitive, the secretions of the prostate and vesicles become altered and symptoms of irritable or atonic impotence, sexual neurasthenia and sterility are added to the clinical picture.

The indications for *treatment* are (1) to cause absorption of the

inflammatory exudate, thereby restoring glandular drainage and function; (2) to destroy the gonococcus.

To accomplish this, the following measures are employed:

- (1) Massage of the prostate and vesicles.
- (2) Dilatation.
- (3) Irrigations and instillations.
- (4) Heat.
- (5) Urethroscopic treatment.
- (6) Operative treatment.

MASSAGE.—The object of **massage** is to expel the purulent material plugging the ducts of the prostatic glands and also to express the accumulated secretions in them.

Technic.—A rubber cot is placed over the index finger. A 2-inch bandage is wrapped around the knuckles to protect them from being soiled. The finger cot is then lubricated with vaselin and gently inserted through the anal sphincter into the rectum.

The prostate is then gently but thoroughly massaged by a side-to-side motion, beginning at the upper borders of the gland and gradually reaching the apex. This manipulation is continued for several minutes if well tolerated.

The vesicles are next treated similarly. The finger reaches up as far as possible and presses upon the vesicle, gradually withdrawing the finger with a to-and-fro lateral motion until the prostate is reached. Special attention should be given to the junction of the vesicles and prostate, because at this point there is usually a deposit of periprostatic exudate. The massage of the vesicles is kept up until there is a distinct reduction in size. Any secretion expelled through the urethra is placed on a slide and examined for pus and gonococci. If well borne, massage can be given three times a week, and is kept up until all pus disappears.

Contra-indications.—Massage should be kept up if it relieves the subjective symptoms. If it increases them, then it is harmful. Massage is dangerous in acute inflammation of the urethra, prostate, vesicles and epididymis. If bleeding follows, the manipulation has either been too severe or there is an acute process, either in the vesicles or in some part of the prostate. When this occurs, massage should be discontinued until bleeding has completely stopped.

DILATATION.—**Dilatation** of the prostatic urethra helps to promote absorption of urethral and periurethral infiltrations.

The instrument most suitable for dilating is the posterior Kollmann dilator. With this instrument, the urethra can be dilated up to 45 or 50 French. Some urologists prefer the irrigating type of the Kollmann dilator. The authors do not employ them. They rust at the joints and get out of order very easily; furthermore, they are hard to keep clean.

Technic.—The instrument should always be covered with a rubber sheath. It is lubricated by dipping into sterile glycerin and gently inserted into the deep urethra. The dilating screw on the handle-end is then turned until the patient complains of pain. At the next treat-

ment, the dilatation is carried one number higher. Usually dilatation up to 40 Fr. is sufficient for most cases. Dilatation is usually tolerated twice a week. Dilatation may be well borne three times a week.

Contra-indications.—When the urine contains free pus or the gonococci persist, dilatation is dangerous. When the urine is only slightly cloudy and contains many shreds, dilatation is most serviceable and practically free from danger. Still one should always remember that if it is too rapidly or too frequently performed, acute prostatitis or epididymitis may result. If excessive bleeding follows, it should not be repeated until the patient has received a course of massage and irrigations.

IRRIGATIONS.—The drug of choice is **silver nitrate**, beginning with 1-8000 and gradually increasing in strength, administered according to the methods previously described.

INSTALLATIONS.—In the terminal stages of chronic posterior urethritis, when shreds and pus still persist in the morning urine, urethroscopic examinations may reveal erosions and granulations in the lateral prostatic sinuses. These usually respond to instillations of **nitrate of silver**, beginning with $\frac{1}{2}$ per cent. and gradually increasing to 3 per cent. If they still persist, stronger solutions applied through the urethroscope are necessary to destroy them.

URETHROSCOPIC TREATMENT.—This form of treatment is occasionally indicated in the terminal stages of chronic posterior urethritis, when granulations, erosions, papillomata and polypoid excrescences are present in the urethra.

The drug employed is **silver nitrate** in strengths ranging from 5 to 20 per cent. The stronger solutions should be carefully applied with cotton mopped around fine applicators, at intervals of 5 to 10 days, the interval depending on the intensity of the reaction.

The Young straight urethroscopic tube is recommended in preference to the beaked posterior urethroscopes of the Swinbourne type.

The previous instillation of 4 per cent. **novocain**, **aposthesin** or **alypin** lessens the pain of the manipulation.

Urethroscopic applications are sometimes useful when the verumontanum remains large and edematous, giving rise to urethral irritability and neurasthenia.

HEAT.—**Heat** is applied to the prostate and vesicles through the rectum, either by means of the **bipolar high frequency current** or the **hot rectal douche**.

Hot rectal douches may be given either with a closed metal tube, the psychrophore, or through a double current tube, of the Chetwood, Guiteras or Tuttle type. The patient fills a two-quart douche bag with water and suspends it about three feet above the toilet seat. He then seats himself and inserts the lubricated tube into the rectum for about four inches and turns on the water. The temperature of the water is usually 120° F. (48.9° C.), or as hot as the finger can bear. The douche should be repeated daily and stopped when the bowel becomes irritated.

Heat may be applied to the prostate by the **D'Arsonval current**. The patient is placed on the table and a thick metal electrode is placed

in the rectum. Another large flat electrode is placed over the suprapubic region. From 800 to 1500 milliamperes may be borne comfortably for 15 to 20 minutes.

OPERATIVE TREATMENT.—In the absence of stricture or abscess, operative procedures are rarely called for in cases of chronic gonorrhea. In order to cure persistent infection of the seminal vesicles, Belfield advocates exposing the vas through an incision in the scrotum. He then incises the vas and injects into the proximal end, either **10 per cent. argyrol** or **4 per cent. collargol** and fixes the duct in the wound so that any discharge will escape through the wound itself and not into the scrotum. The object of the operation is to secure antisepsis and drainage of the vesicles. Excellent results are claimed by him from this operation. Fuller recommends **vesiculotomy** through a perineal incision. There is no doubt that his operation unquestionably relieves the rheumatic pains in a great many cases; on the other hand, it frequently fails. Cabot recommends **vesiculectomy**, claiming that it is impossible to drain a tortuous tube like the vesicle by simple incision. The objection to his operation is that it is very frequently followed by impotence.

Experience has shown that these operative procedures should be employed only in intractable cases after every other method has been thoroughly tried out.

ROUTINE TREATMENT OF CHRONIC POSTERIOR GONORRHEA.—The type of treatment will depend upon whether the second urine is clear, with shreds, or slightly cloudy (due to small amounts of free pus).

In the former instance, when the urine is clear but contains many shreds, the treatment is begun with **silver nitrate irrigations** given through a catheter (*see* page 483), beginning with 1:8000. These irrigations are given every other day. Usually after a week massage may be begun.

The patient reports with a full bladder. He voids the first half of the urine in two glasses. The prostate and vesicles are then gently but thoroughly massaged, after which the patient voids the remainder of the urine. The urines are examined. The treatment is completed by an irrigation of nitrate of silver. Some urologists inject **argyrol** into the bladder or distend it with the silver solution, claiming that it is easier to massage the vesicles and prostate when the bladder is full and also that epididymitis is prevented in this way. The authors find this preliminary antisepsis unnecessary and cumbersome. Furthermore, it is much more trying to the patient to be massaged when the bladder is filled with silver solution.

When the urine clears up and it is seen that local treatment is well tolerated, **dilatation** may be begun. The routine is as follows:

Having massaged the prostate and vesicles, as previously described, the patient is placed on the table. The Kollmann dilator, properly lubricated, is introduced and dilatation performed until pain is complained of. The dilator is then gently withdrawn, after which an irrigation of silver nitrate is given.

The intervals between treatments will depend entirely upon the tem-

per of the urethra. Some patients tolerate treatment three times a week, others less often. If dilatation causes most irritation, it should be given less often than massage and irrigations. In all cases, the treatment is not repeated until all reaction from the previous one has ceased.

If symptoms of over-treatment occur, as shown by increasing cloudiness of urine and irritability of the urethra (frequency and precipitancy of urination), all local treatment is stopped until they have subsided.

When the second urine contains much free pus, it is safer to begin the treatment with the **organic silver salts**, preferably **argyrol** 20 per cent. freshly prepared. **Instillations** are given every day. When the urine becomes almost clear, and it is determined that local treatment is tolerated, then the local treatment previously described is cautiously begun.

(3) **Chronic Anteroposterior Gonorrhea.**—When the infection involves the anterior as well as the posterior urethra, it is impossible to outline a routine method which will apply to all cases, because it is sometimes difficult to decide, in the beginning, which of the various lesions along the urethra or in the prostate is the important one requiring immediate attention. It is important, however, to bear in mind that whatever form of local treatment is given it should be for the definite purpose of curing a known lesion. The effect of treatment should be closely watched. Unless improvement is noted, the treatment must be changed. To the beginner, the management of these cases is at times perplexing and disappointing.

The various therapeutic procedures have already been described in detail; their proper application will depend entirely upon the experience and judgment of the physician.

(4) **Acute Exacerbations of Chronic Gonorrhea.**—The management of these cases will depend entirely upon the symptomatology, physical signs and urinary findings. At times, they simulate acute anterior urethritis, others appear as acute posterior infections, while a third variety shows symptoms of both acute anterior and posterior involvement.

COMPLICATIONS OF GONORRHEAL URETHRITIS AND THEIR TREATMENT

Genito-urinary Complications.—**FOLLICULITIS.**—As a result of supurations of one or more urethral follicles, retention of pus may occur, forming small abscesses. These usually escape notice during the acute stage of the disease. When they occur during the declining stage, they cause a characteristic return of symptoms. After a day or two of indefinite localized itching or uneasiness, the discharge, which previously was very scant and mucoid in character, becomes profuse and purulent. The meatus may even become inflamed. The characteristic feature of the discharge is that it lasts but a short time, and stops as suddenly as it began.

Treatment.—During the acute stage no special treatment is required.

The usual local treatment of urethritis, if persisted in, will nearly always clear up the abscesses. The treatment of acute relapses of chronic folliculitis will be considered under chronic urethritis.

PERIURETHRAL ABSCESS.—The suppurative process from an infected urethral gland may extend to the periurethral connective tissue. These abscesses usually appear alongside the frenum, in the pendulous portion, or in the perineum, in which case Cowper's glands may be involved. Abscesses forming beside the frenum grow rapidly. They either open spontaneously or require **incision**. In either case, they may close spontaneously or require special treatment for their cure. When the resulting fistula shows no tendency to close it should be injected with a **25 per cent. ethereal solution of hydrogen peroxid**, preferably through the urethral end. This may be repeated every three days until the fistula closes. If it does not yield to this treatment, a **plastic operation** is necessary.

Periurethral abscess of the pendulous portion usually develops quite slowly. It either resolves or ruptures into the urethra. More frequently, it invades the skin and points directly opposite the point of origin. More rarely, the pus may travel beneath the fascia for a considerable distance before rupturing externally, unless promptly excised. The fistulas, unless large, heal spontaneously. The *treatment* consists in laying the abscess cavity **open freely** as soon as fluctuation is noticed, evacuating the pus and allowing it to heal by granulation.

In abscess formation in Cowper's glands, the abscess usually appears on one side of the median line. The pus may travel some distance beneath the deep fascia before breaking through, causing extensive perineal infiltration, and frequently multiple persistent fistulas. The treatment is **wide and free excision**.

SPONGEITIS AND CAVERNITIS.—Inflammation of the erectile tissues is an extremely rare complication of gonorrhea. The treatment consists of **rest in bed, hot or cold applications**, and **incision** if abscess occurs.

INGUINAL ADENITIS, LYMPHANGITIS.—These complications are due to the extension of the gonorrhea beyond the urethra. The adenitis consists of an inflammatory enlargement of the glands in the groin, which rarely suppurate.

Special *treatment* is rarely necessary. If marked, or if pain is present, the patient is **put to bed** and **heat or cold** applied. Painting the skin over the gland with **iodin** and applying a **glycerin compress** seems to hasten resolution and relieve pain in severe cases. If supuration occurs it should be treated as bubo.

BALANITIS.—This consists of an inflammation of the mucous membrane of the prepuce and glans penis. It occurs in men with long foreskins and in persons of uncleanly habits.

The *treatment* consists in **bathing** the parts with soap and water. If much inflammation and discharge are present, a small pledget of cotton is soaked in **lotio nigra**. This is placed around the glans and the foreskin is drawn over it. Later the following **dusting powder** is used:

R	
Bismuthi subnitratiss	}āā 3ii (8.0 grams)
Calomel	
Acidi borici	
M. Ft. Pulv.	

Sig.: Apply externally.

Sometimes the swelling of the foreskin is so great that it cannot be retracted. This condition is called *phimosis*. The treatment consists in **prolonged soaking** of the penis in **hot water**. The patient should also be instructed to inject **protargol** $\frac{1}{4}$ per cent. under the foreskin. If the swelling and edema persist or if gangrene threatens, an **incision** is made through the prepuce on its dorsal aspect. This can be done painlessly under local anesthesia. Sometimes a long and tight prepuce is caught behind the glans and cannot be drawn over it. This is called *paraphimosis*. The treatment consists in drawing the foreskin over the glans by **manipulation**. In severe cases, preliminary prolonged soaking in hot water facilitates the reduction. If it is impossible to accomplish this, the constricting band should be incised on the dorsum, which generally permits prompt reduction.

ACUTE PROSTATITIS AND PROSTATIC ABSCESS.—Acute gonorrheal inflammation of the prostate occurs in all degrees of severity. The prostatitis may be so mild as to add scarcely any symptoms to those of urethritis. When there is marked involvement, definite constitutional and local symptoms are present. Since acute prostatitis cannot be differentiated from prostatic abscess they will be considered together.

Increase in Local Symptoms of Posterior Urethritis.—In addition, the patient complains of a dull aching or throbbing pain, which is felt either in the rectum, hypogastrium or in the pelvis, radiating down to the testicles and thighs.

Dysuria.—In addition to frequency and urgency of urination, the urinary stream is smaller and weaker. It may be intermittent. In marked enlargements, complete retention may occur. Defecation may be painful and difficult.

Chills and Fever.—Very often a severe chill ushers in the febrile period. The degree of fever is no index, however, to the degree of the prostatic involvement. Quite frequently, there is an absence of fever in severe cases.

Local Signs.—One or both lobes of the prostate are always enlarged. When the whole gland is involved, it may become so large that it is impossible to reach its upper border with the examining finger. The gland feels hot, hard and is tender to the touch.

Resolution may occur or the inflammation may become chronic. The abscess may rupture into the urethra, rectum or into the periprostatic tissue, causing ischiorectal abscess.

Most prostatic abscesses, fortunately, rupture into the deep urethra. Sometimes they point into the rectum or perineum. In rare instances, the pus, burrowing forward into the perineum, extends along the corpus

cavernosum, causing considerable infiltration and slough. It has been known to follow the various fascial planes and point in the inguinal canal and even in the space of Retzius, in neglected cases.

Treatment.—As soon as the complication is recognized, all urethral treatment is stopped. In mild cases the treatment is that of acute posterior urethritis. **Hot rectal douches** are ordered twice a day. **Vaccines** are indicated. Their prompt administration may sometimes prevent or abort abscess formation.

In severe cases, where there is much urinary distress and fever, the patient is **put to bed** and a **hot-water bag** applied to the perineum. Hot rectal douches are given every four hours. To relieve the urgency and tenesmus attending urination, the following **rectal suppository** will be found useful:

R

Morphinæ sulphatisgrain $\frac{1}{4}$ (0.016 gram)

Quininæ sulphatisgrains x (0.65 gram)

Olei theobromatis..... q.s.

M. Ft. Rectal suppositories.

Sig.: Insert 2 to 3 times a day.

If there is acute retention, the bladder is emptied with a soft rubber catheter, size 12 to 14 French, every six hours, after which $\frac{1}{2}$ ounce (15 c.c.) of **10 per cent. argyrol** is instilled into the bladder and deep urethra. If, in spite of this treatment, acute retention is not relieved in a few days, or if the temperature remains high and there is prostration, **surgical interference** is indicated. Opening the abscess through the perineal route gives prompt relief, thereby preventing the miserable and even fatal results following prolonged palliative treatment.

SEMINAL VESICULITIS.—Acute seminal vesiculitis always occurs in conjunction with acute posterior urethritis and prostatitis. It usually adds nothing to the symptomatology, except that in rare instances, when there is a marked unilateral involvement, the patient may complain of pain in the groin or in the lumbar region on the corresponding side. Occasionally, a rather profuse terminal hematuria ushers in a vesiculitis.

By rectum, the vesicles feel thickened, hot and very tender. If there is pus retention, a tense sausage-like tumor is felt above the prostate on one or both sides. The abscess usually terminates by resolution, but may rupture into the rectum, peritoneum or ischiorectal fossa.

Treatment.—The treatment of acute seminal vesiculitis is the palliative treatment of acute prostatitis. If an abscess forms and shows a tendency to spread, **vesiculotomy** is indicated.

EPIDIDYMITIS.—Inflammation of the epididymis is caused by the passage of gonococci from the posterior urethra through the vas deferens, or by extension of the inflammation along the lymphatics of these canals.

The inflammation is usually limited to the epididymis, although the testicle is often apparently enlarged, because it is surrounded by the inflamed epididymis. Frequently, there is an effusion of serum in the

sac of the tunica vaginalis, causing the testicle to appear larger than normal.

Etiology.—The direct causative factor is invasion by the gonococcus. Some patients are more prone to epididymitis than others, because, in spite of every precaution, this complication will occur; while others, disregarding all hygienic precautions, go about with an acute gonorrhea, indulge in sexual excesses and alcohol and yet escape. Abortive and strenuous local treatment are, very frequently, exciting factors.

If the modern moderate local treatment is properly administered and if the patient wears a well-fitting suspensory bandage and abstains from violent exercise—horse-back riding, dancing, sexual excitement and the use of alcohol—in most instances he will escape this complication.

Pathology.—The inflammation begins in the globus minor. If mild, the infection is confined to this end of the epididymis. If severe, it may extend throughout the organ, causing infiltration, hardening and enlargement with the formation of focal abscesses. The tunica may become acutely inflamed and hydrocele result, but the testicle rarely takes part in the inflammation. The vas deferens may be slightly thickened and tender.

Symptoms.—An indefinite dragging sensation is first felt in the testicle, radiating upward into the groin. Pain and swelling of the epididymis comes on rapidly. Within a few hours, the epididymis is large, hot and exquisitely tender. The scrotal tissues may become red, thickened and edematous. The inflamed mass may reach the size of a fist. Standing, walking, bending or lifting aggravates the pain.

The urethral discharge usually disappears or diminishes noticeably with the onset of the epididymitis, only to reappear again when the inflammation subsides.

Examination shows the epididymis enlarged, hard and tender. The testicles cannot be outlined. The spermatic cord is thickened and tender.

Prognosis.—As the inflammation advances, the pain and swelling increase in intensity. Within a few days the symptoms gradually subside. Resolution begins rapidly, but progresses more and more slowly, until it seems to remain stationary. The globus minor is the last to clear up. The little hard lump in the epididymis known sometimes as the “gonorrheal nodule” may be permanent. It causes no uneasiness and is not sensitive to pressure.

There is no danger to life, sexual desire or potency. Sterility of the affected side is not uncommon. Relapses may occur. If both sides have been affected, sterility may be caused by the formation of a permanent inflammatory infiltrate, plugging up or compressing the efferent duct of the epididymis. Atrophy of the testicle never occurs, unless there has been an accompanying orchitis.

Treatment.—Much can be done to avoid this complication by using the utmost care and gentleness in the treatment of posterior urethritis. Vigorous local treatment when begun too soon, or rough instrumentation, may be exciting factors.

The patient should be instructed to wear a proper-fitting suspensory

SCROTAL SUPPORT.

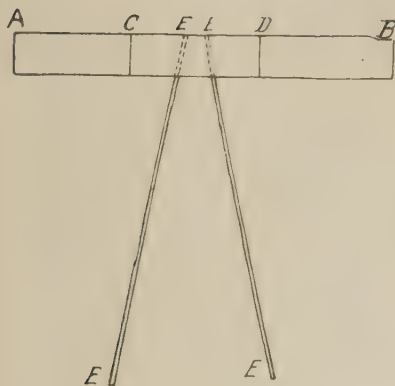


FIG. 5a



FIG. 5b

This support devised in Bellevue Hospital and made of adhesive will be found far superior to any jock strap or suspensory on the market. When properly applied the patient can attend to his work in comparative comfort.

It consists of a strip of adhesive plaster thirty inches long and three inches wide A-B. At a point near the midline are attached two strips of plaster one half inch wide and twenty inches long E-E. To prevent the plaster from adhering to the scrotum, a shorter strip eight inches long and three inches wide C-D is applied to the middle portion of A-B. The strip A-B acts as a sling for the scrotal contents, as shown in Fig. 5 b, the exposed adhesive side being applied to the sides of the abdomen. The patient lies on his back while the surgeon holding the scrotum well up towards the abdomen with one hand adjusts the support as in Fig. 5 b, after which the strips E-E are drawn backward between the thighs and well around them. These serve to hold the sling in position, preventing it from slipping forward. The support is reinforced by additional strips similar to A-B, and several more transversely placed above the symphysis. Before applying the plaster the scrotum is covered with absorbent cotton or gauze.

during the acute stage of the gonorrhea. This measure certainly reduces the danger of epididymitis.

The treatment consists of **rest in bed, support and elevation of the testicle, local applications, internal treatment and vaccines**. Although mild cases do not require rest in bed, this should be insisted on whenever possible. If for various reasons it cannot be carried out, the patient is advised to wear a snug-fitting support. The following ointment is of service: Ichthyol, \mathfrak{ss} (15.0 c.c.); lanolin \mathfrak{ss} (30.0 c.c.); vaselin, \mathfrak{ss} (30.0 c.c.).

The ointment is spread over lint, and applied to the testicle. A layer of cotton is spread over the lint and the scrotum is supported by a suspensory. **Vaccines** are given every other day.

All local treatment of the urethra is stopped and not resumed until the inflammation in the epididymis has quieted down. Severe cases require **rest in bed**. The testicles are supported by a **suspensory**, or if this is inadequate, a strip of adhesive plaster, 4 in. x 20 in., is stretched across both thighs under the scrotum.

To most patients the application of cold in the form of an **ice bag** is preferable to heat. It is immaterial, however, whether **heat** or **cold** is applied, providing it gives relief.

Various local applications are recommended. The authors prefer the **ichthyol ointment** previously described. The application of 10 per cent. **guaiacol** in glycerin or olive oil relieves pain, but is objectionable on account of its odor. We have never seen much benefit derived from the old-time **tobacco poultice** or **Tucker's saturated solution of magnesium sulphate**. **Strapping of the testicle** was formerly the routine treatment, and many patients can testify to the agonizing pain caused when the plaster was too snugly applied. It is of doubtful value, and never of any value unless employed in the ascending stage of the inflammation. The authors have long discarded it.

Diathermy.—The application of heat to the inflamed epididymis by means of the d'Arsonval current is a very useful therapeutic measure. It almost always lessens the severity of the symptoms and in some cases shortens the course of this complication. If applied at the onset it sometimes will abort the attack. Corbus and O'Connor have devised a clamp for applying the current to both sides of the involved organ. In order to get the best effect, the current is increased to a point just short of cutaneous discomfort. The duration of each application should not be less than forty minutes.

Operative Treatment.—Francis R. Hagner developed the operative treatment of acute epididymitis. His operation consists of incision of the layers of the scrotum and exposure of the epididymis. Multiple punctures are then made in the infiltrated areas. A cigarette drain is inserted and the wound closed.

Hagner claims that, by his operation, relief of pain is immediate and that there is less danger of sterility. The experience of most urologists is that, although relief from pain is immediate, convalescence is longer than with the non-operative treatment. Regarding its effect upon sterility, the statistics supporting this claim are not sufficiently large to substantiate it. The writers reserve this procedure for intractable cases

only, which do not yield to treatment, and for persistently recurring cases.

RENAL INFECTION.—Renal infection due to gonorrhea is rare. Pyelonephritis may occur in very severe cases. Usually it is mild in its course. The treatment is similar to that for pyelonephritis due to other bacteria.

Bones and Joints.—**GONORRHEAL RHEUMATISM.**—The term, “gonorrheal rheumatism,” includes all metastatic gonococcal inflammations involving the synovial membranes of joints, tendon sheaths, bursæ, etc.

Occurrence.—Different observers have estimated that rheumatism occurs in from 2 to 8 per cent. of cases of gonococcal infection. It is difficult to arrive at anything approaching an accurate conclusion, especially in those cases where there is an apparent absence of local genital or urethral infection, because so many cases of gonococcal rheumatism are not diagnosed, as such, owing to lack of knowledge or to suppression of a previous history of gonorrhea.

Males are more liable than females. In young girls and children, the tendency to rheumatism is more pronounced than in adult females; it may follow vulvovaginitis or ophthalmia neonatorum.

One or several joints may be affected. In order of relative frequency, the joints involved are the knee, ankle, wrist, fingers and great toes, elbow, shoulder, hip and jaw. Tenosynovitis and periarticular involvement should excite suspicion as to the nature of the inflammation.

Pathology.—The gonococcus reaches the synovial membranes by the blood stream. Round-cell infiltration of the tissues, edema and serofibrinous effusion follow. Later, adhesions are produced which limit the movements of the parts. The inflammation may go on to pus formation. Secondary infection by staphylococci or streptococci may supervene, in which case, erosions of the cartilage and destruction of the joint may be expected.

Clinical Forms.—Clinically, the following types are met with:

- (1) *Arthritic*, in which one or several joints may become involved.
- (2) *Hydrarthrosis*, usually monarticular, particularly liable to involve the knee.

(3) *Bursal or synovial form*, in which the tendons and their sheaths, bursæ (e.g., of the patella, the olecranon or the tendo achillis) and periosteum are involved. The articulations may not be affected.

(4) *Arthralgic*, in which there are wandering joint pains with or without redness and swelling.

Keyes employs the following classification:

(i) *Gonorrheal arthritis*, in which the organisms are located in the joint itself, and

(ii) *Gonorrheal osteo-arthritis*, in which the gonococci are localized in the articular extremities of the bones, and any effusion into the joints is secondary.

Symptoms.—In the acute type the onset is sudden, the temperature rising to 103° F. (39.4° C.). The inflammation begins like an attack of acute articular rheumatism, with redness, swelling, extreme tenderness

and loss of function. There is usually some effusion into and around the joints. In severe cases, the tendon sheaths and bursæ become involved, with increase of the effusion in the joint and also periarticular edema. The onset may be subacute, with local pain and tenderness and moderate to severe disability. The duration of the attack is usually long. The mildest lesion may persist for months.

Diagnosis.—When acute rheumatism occurs during the course of gonorrhea, the diagnosis is not difficult. Marked swelling of a joint, with periarticular involvement, giving a fusiform appearance to the joint, and a positive complement-fixation test fix the diagnosis.

Chronic gonorrheal arthritis is differentiated from other forms of arthritis by means of the complement-fixation test.

When acute rheumatism occurs, in cases with no history of gonorrhea or apparently no urethral or genital lesion, in which there is no perspiration and no response to the salicylates, the serum reaction will prove of service in making a diagnosis.

Sometimes the gonococcus can be identified in the fluid aspirated from the joint. Frequently, the fluid does not yield the organism. In addition, a careful routine examination should be made of the urinary and genital tracts.

Treatment.—Proper local and internal treatment of the urethritis is the best prophylactic. If fever appears during the course of a gonorrhea, the administration of **vaccines** may possibly have a prophylactic action.

With the onset of the attack, the patient is **put to bed**. For the relief of pain, the **joint** is **immobilized** with a light splint, preferably of plaster-of-Paris. The **Bier treatment**, or exposure of the joint to **hot air**, should be employed. If the pain is severe, applications of equal parts of **ichthyol** and **glycerin** may afford relief. When the pain is very severe, stroking the joint lightly with the **actual cautery** frequently gives immediate relief.

The use of **vaccines** in some cases often gives definite and satisfactory results; in others, the results are entirely negative.

The tendency to the formation of adhesions must be kept in mind and gentle **passive motion** employed to prevent ankylosis, remembering, however, that too early or too forcible passive movements may light up a subsiding inflammation.

The usual **antirheumatic remedies** are usually quite useless.

The **diet** should be ample and similar to that in chronic gonorrhea. Restrictions are not necessary.

Systematic gentle **massage**, in the subsiding stages of the inflammation, helps to diminish the muscular atrophy occurring in the prolonged chronic cases.

If the effusion into the joint is not arrested by immobilization and baking, the **fluid should be aspirated** under the most careful asepsis. In most cases this is unnecessary. Fuller advises **seminal vesiculotomy** in these cases on the ground that the local focus, which causes systemic infection, is present in the seminal vesicles. The precise status of this

operation, in the treatment of gonorrheal rheumatism, is not yet definitely established. In some cases it succeeds, in others it fails.

The prostate and vesicles should be gently and thoroughly massaged every day unless they are acutely inflamed. Resulting deformities and loss of function are treated by **orthopedic methods**.

EXOSTOSIS OF THE OS CALCIS.—The inflammation begins as a periostitis or myositis at the attachment of the flexor brevis digitorum to the tubercle of the os calcis. When the acute inflammation subsides, an exostosis forms. Pressure upon this while walking causes great pain. The diagnosis is made by radiography. The treatment is chiseling away of the exostosis through an incision along the inner side of the heel.

Gonococcal Affections of the Heart and Blood-vessels.—**ENDOCARDITIS.**—Ricord in 1847, and Brandes in 1854, were among the first to recognize that endocarditis could be caused by gonococci circulating in the blood of susceptible patients suffering from gonorrhea. In 1895, Thayer and Blumer cultivated the gonococcus from the blood of a patient suffering from acute endocarditis.

Pathology.—No characteristic feature has been described which would differentiate the gonococcal from other forms of endocardial inflammations. Vegetations composed of fibrin and infiltrated with leukocytes and gonococci, erosions, ulcerations and valvular destruction are found. The *diagnosis* is dependent on the isolation of the gonococcus. A few cases, in which streptococci and staphylococci were found in conjunction with gonococci, have been reported.

Symptoms.—In most cases, the symptoms are less acute than in ulcerative endocarditis due to other organisms. Temperature ranges from 101°-103° F. (38.3°-39.4° F.). Dyspnea, precordial distress and palpitations are present. Sooner or later, the usual auscultatory signs appear. The lesions are usually confined to the left side of the heart. The relative frequency in which the various valves are involved is as follows:

Mitral, 48 per cent.

Aortic, 39 per cent.

Pulmonary, 5.3 per cent.

Tricuspid, 2.6 per cent.

Embolie metastasis may involve the spleen, liver, kidneys, etc. Men are more frequently attacked than women, and women are more susceptible during pregnancy and the puerperium.

Treatment.—The treatment will be described under septicemia.

PERICARDITIS.—This occurs very infrequently. The amount of effusion is seldom great. In rare cases, aspiration was required to relieve the dyspnea. The fluid may be serous, serofibrinous or purulent.

PHLEBITIS.—The prostatic plexus of veins and the pampiniform plexus of the spermatic cord and of the broad ligament are the most common areas to be primarily affected.

Treatment.—In addition to the care of the genital focus and of the septicemia, **complete rest** of the affected parts should be secured.

GONOCOCCAL SEPTICEMIA.—The first to separate the gonococcus from

the blood stream was Hewes, who, in 1894, isolated the organism from the blood obtained from a case of gonorrheal arthritis.

Lofaro believes that the gonococcus reaches the blood through the lymphatics, but in some cases direct entry into a blood-vessel, associated perhaps with venous thrombosis, is the origin of the systemic infection. Owing to a deficiency in the resistance of the individual, septicemia results, which may either run a short acute course ending in recovery or death, or it may become chronic, with a liability to acute exacerbations.

Predisposing Factors.—Among these are traumatism, caused by unskillful instrumentation, alcoholic and sexual excess, menstruation, pregnancy and any general condition lowering the power of resistance, such as tuberculosis and diabetes.

Symptoms.—In acute cases the symptoms are similar to those of sepsis caused by any pathogenic microorganism. The temperature may resemble typhoid fever or pyemia. The spleen is frequently enlarged, and the liver may be felt below the costal margin or it may be atrophied with symptoms of jaundice. Albuminuria and cutaneous eruptions or petechia may be present.

In very severe cases, there is headache, thirst, profuse perspiration, vomiting, diarrhea and death.

In chronic cases, the symptoms are much less severe and sometimes the condition is mistaken for toxemia.

Diagnosis.—The diagnosis is wholly dependent upon the isolation of the organism from the patient's blood.

Complications.—Arthritis is the most frequent complication. The most important one is endocarditis. Pericarditis, meningitis, pneumonia, peritonitis, pleurisy, iritis, conjunctivitis, thrombosis and embolism may occur.

Prognosis.—The prognosis will depend upon the intensity of the septicemia and the gravity of the complications. It should always be guarded in acute cases, because of the difficulty in stimulating the formation of antibodies, and in subacute cases because of the danger of serious complications.

Treatment.—The first indication is to **open and drain** any abscess cavity, however small, providing the patient's condition permits it.

The temperature, if high, may be controlled by **alcohol sponging, cold packs or baths**. The diet should be sustaining and easily assimilated. **Alcohol** is contra-indicated. **Antigonococcic serum** seems of more value than vaccines in acute cases. An injection of 15 to 25 c.c. every four hours is given.

In chronic cases, **vaccines** are said to be more beneficial. Satisfactory results have been reported with the **intravenous injection of colloidal silver** given in doses of 10 c.c. every three or four days.

Complications arising during the course of the septicemia should be treated along the usual lines.

Gonococcal Infections of the Eye.—The eye may become infected

with the gonococcus either through direct inoculation from without or through the blood stream.

Etiology.—The great majority of cases are due to accidental contamination of the conjunctiva either from handkerchiefs, towels, hands or during the passage of the child through the genital tract of the mother infected with gonorrhea.

Infants are especially susceptible to gonorrheal conjunctivitis. Since the conjunctivitis of infants, known as "ophthalmia neonatorum," differs in some respects from the disease as seen in adults, it will be considered separately.

OPHTHALMIA NEONATORUM.—When the infant's eyes are infected in the parturient canal, the infection usually occurs while the eyes are passing over the perineum, as the lids at this moment are most liable to become separated.

Infection may take place in utero, the organisms in this instance penetrating into the amniotic fluid, in which case the child is born with a well-developed ophthalmia. Cases have been reported in which the eyes were completely destroyed at birth.

Inoculation of the eye is very liable to occur during the cleansing immediately after birth. Gonococcal pus from the cervix, adhering to the child's face, may be washed into the eye by the nurse or rubbed into it by the hands of the infant.

Symptoms.—Evidence of the disease is usually present in the first 48 hours. The earliest symptoms are those of irritation, viz., redness of the conjunctiva and excess of serous secretion. The redness increases and spreads and the lids become intensely red and swollen. The secretion rapidly becomes purulent and glues the lids together. On separating the lids, pus freely exudes. In untreated cases, the inflammation goes on to ulceration of the cornea with sloughing, resulting in opacities and defective vision or even total blindness. In many cases the whole eyeball may be completely destroyed.

Diagnosis.—Almost every inflammation of the infantile conjunctiva of increasing severity and associated with the formation of thick profuse pus is gonorrheal. The microscope determines the diagnosis.

Prognosis.—The prognosis depends entirely upon the stage at which the disease comes under treatment. If sloughing ulcers of the cornea are present, there is always some impairment of vision. In children suffering in addition with congenital syphilis the outlook is very grave.

Prophylaxis.—At birth a germicide should be dropped into the eyes of every child. There should be no exception to this rule of practice. Cr  d   recommended 2 per cent. **silver nitrate**. Many observers, notably Stephenson, find that 1 per cent. silver nitrate is equally efficient. Others employ the **organic silver salts**. Darier, of Paris, uses 15 per cent. freshly prepared **argyrol**. Others use protargol 3 to 5 per cent.

Treatment.—**Cold applications** form an important part of the treatment. They must be kept up night and day. Thin pads of gauze, chilled in ice water, are placed over the closed lids. These are re-

newed every five minutes day and night. If the cold is too intense, the nutrition of the cornea may be interfered with, evidenced by a misty or cloudy appearance beginning at the center. When this occurs, the cold should be stopped at once and not renewed until the cornea clears up.

In addition, a few drops of 20 per cent. freshly prepared **argyrol** are dropped into the inflamed eye every hour. When the inflammation begins to subside and the discharge becomes mucopurulent, a 1 per cent. **silver nitrate** solution is applied once a day, until no gonococci can be found in the secretions.

If only one eye is involved, every precaution should be taken to protect the healthy eye. Various methods have been employed. Knapp employs a **mica spectacle plate**, which can be obtained from any optician. It is transparent, light and does not steam. It is fastened on with adhesive strips.

GONOCOCCAL CONJUNCTIVITIS IN THE ADULT.—The incubation period is about three days. The onset is hyperacute and there is pronounced pus formation. Corneal complications are more frequent and more severe than in infants. Chemosis, rare in the infant, is a feature of the disease in the adult. When pronounced, early and dangerous forms of ulceration may be anticipated.

Treatment.—The treatment is the same as in infants. When the cornea is involved, **atropin** $\frac{1}{2}$ per cent. or **eserin** is employed.

Vaccines and **sera**, in the infant and adult types, are employed by many as a routine measure. In most cases they have not proven successful.

SYSTEMIC OCULAR GONORRHEA.—Byers enumerated the various lesions that may occur as a result of systemic metastatic infections as follows: iritis (Mackenzie), conjunctivitis (Fournier), iridochoroiditis (Koeniger), keratitis (Colsmann), panophthalmitis (Martin), optic neuritis (Panas), retinitis (Burekhardt) and thrombosis of the retinal vessels (Galezowski).

Iritis or iridocyclitis may appear as a feature of systemic gonorrhea. It shows a tendency to recur with each attack or relapse of urethritis. It is usually mild, in which case it is frequently overlooked, or it may be severe and compel attention.

Conjunctivitis is nearly always bilateral.

Symptoms.—The symptoms are much milder than in cases due to direct inoculation. Gonococci are usually found in the discharge. The average duration is two weeks and the prognosis is good.

When the retina is involved, the lesion is a neuroretinitis which may be unilateral or bilateral. In nine cases reported by Byers, six recovered and three terminated in atrophy.

Diagnosis.—Systemic ocular disease is more likely to be mild, bilateral and is always associated with genital gonorrhea and gonorrheal arthritis. The finding of the gonococcus in the ocular disease and a positive fixation test prove the nature of the lesion, but may leave doubt as to whether the eye condition is local or metastatic.

Treatment.—Conjunctivitis is treated as described in the foregoing

section. Other local treatment is along general lines; e.g., **atropin** for iritis, etc. The genital gonorrhea should be vigorously treated. **Vaccines** and **sera** may be administered but are of doubtful value.

Buccal and Nasal Gonorrhea.—Ahlfeld and Kimball have reported cases proving the existence of gonorrheal inflammations of the mouth and nose in infants. In the adult the evidence of its existence is very inconclusive.

In infants, the inflammation is confined either to the nose or mouth and is severe in character. In some cases the nasal gonorrhea has accompanied ophthalmia neonatorum.

Treatment.—Buccal gonorrhea readily clears up with the use of antiseptic mouth sprays, e.g., **Dobell's solution**, **boric acid**, etc.

Nasal gonorrhea is treated with argyrol 20 per cent. dropped into the nose three times a day.

Gonorrhea of the Anus and Rectum.—*Etiology.*—The anus and rectum are relatively quite resistant to gonococcal infection. In 1037 cases of genital gonorrhea collected by Howard, Baer and Schultz, the anus was implicated 157 times. In men, sodomy is accepted as a cause for anal gonorrhea. In women, inoculation occurs from the vulvar discharge or from the douche tube or hands.

Pathology.—The epithelium of the rectum is eroded, infiltrated and ulcerated. Fissures and condylomata are common.

Symptoms.—Usually the symptoms are slight, and frequently overlooked. In the severe cases there is intense itching and burning. Rectal pain and blood-streaked stools are noted when ulcerations are present. Locally, the anal orifice may be swollen or fissured. Condylomata may be present. Pus can sometimes be expressed by pressure from the rectum. Rectal inspection may reveal tumefaction, erosion and ulceration.

Diagnosis.—The diagnosis is confirmed by the microscope, and culture should be done in doubtful cases.

Treatment.—Early cases are treated by injections of $\frac{1}{2}$ ounce of **20 per cent. argyrol** twice a day. Erosions and ulcerations should be **cauterized** every 3 or 4 days with **silver nitrate**, 10 per cent. to 15 per cent.

DETERMINATION OF A CURE

In cases of acute gonorrhea, it is usually quite easy to decide when a cure has been accomplished; in chronic gonorrhea, the decision is much more difficult. In fact, scarcely any two authorities agree as to the procedure to be followed or the facts to be relied upon in determining a cure.

Up to a few years ago, clinical evidence was all that we had to rely upon to decide whether or not gonococci were still present. Experience has shown that such evidence was very often insufficient, to say the least. Very often, the over-cautious physician has forbidden a man to marry when he was perfectly fit to do so, just because a few shreds persisted in the urine or a non-infectious discharge occasionally ap-

peared. On the other hand, others were allowed to marry who later infected their wives, with results that need not be dwelt upon.

To-day, bacteriology has supplied us with certain tests, which when performed by competent bacteriologists, and considered in conjunction with the clinical evidence, gives us an exact method in deciding this important question.

Clinical Facts.—In view of the prevalence of gonorrhea, it may be accepted, as a general rule, that whenever there is an urethral discharge or pus in the urine, gonorrhea should be suspected. On the other hand, if the urine is free from pus and shreds, gonococcal infection in all probabilities does not exist.

Thus, if a patient continues to have pyuria and is subject to relapses of urethral discharge, he is in the majority of cases still infectious. If he is not subject to relapses after sexual or alcoholic excesses, in all probability he is no longer infectious, even if, at times, a slight discharge is present or shreds appear in the urine.

If, after having had gonorrhea, there is no discharge, pyuria or relapses and no pus can be detected in the urine voided after massage of the prostate and vesicles, one is certainly safe in pronouncing a cure. The presence of shreds in the urine does not signify the presence of gonorrhea. Many men have shreds in the urine who have never had gonorrhea.

The writers employ the following routine in deciding whether or not a patient is cured.

1. **Provocative Test.**—*Technic.*—The urethra is dilated with an antero-posterior Kollmann dilator after which a one per cent. silver nitrate instillation is made in the interior and posterior urethra. The patient is then provided with glass slides to collect the resulting discharge for microscopie examination.

2. The next day the prostate and vesicles are thoroughly massaged upon a full bladder. If any secretion is expressed, part of it is caught on a glass slide and stained, the remainder is transferred to a culture tube. The patient is then told to void into a sterile bottle. The urine after massage is then examined for gonococci and also cultured.

3. **Examination of Condom Specimen.**—Whenever possible a condom specimen of the semen should be obtained and stained and cultured for gonococci.

4. **Complement-fixation Test.**

GONOCOCCAL INFECTION IN THE FEMALE

Occurrence.—The prevalence of gonorrheal infection in women varies within wide limits according to different observers. This great difference of opinion may be accounted for in several ways, viz.: (1) the difficulty of finding the organism in chronic cases, (2) the class of

patients treated. In prostitutes, for example, one would expect to find gonorrhea most prevalent. Among 533 prostitutes examined by Huber, 59.6 per cent. had gonorrhea. Among 407 prostitutes, Prowe found gonorrhea in 76.6 per cent. In private practice, Zweifel estimated that the number of women ill because of the gonococcus ranged from 10 to 11 per cent. According to Taylor, the gonococcus is the causative factor in 12 per cent. of all uterine disease.

Gonococcus infection is not uncommon in little girls, especially in institutions.

Organs Invaded.—The urethra, vulva, vagina, cervix, uterine canal and tubes are usually affected. Destructive inflammation of the tubes and ovaries with involvement of the peritoneum is very common. Ascending infection of the urethra, involving the bladder, ureters and kidneys, is by no means rare. Invasion of the rectum may also occur.

Skene's glands and Bartholin's glands frequently become the seat of a chronic gonorrhea. When the ducts of the latter are involved, they appear as two small reddened spots which have been called the "maculæ gonorrhoeicæ" of Sängcr.

In systemic gonorrhea the same organs are invaded as in the male.

Symptoms and Clinical Course.—The incubation period varies from two to seven days. The disease begins most frequently in the urethra. Skene's glands, lying just within the urethral meatus, and Bartholin's glands, just at the entrance of the vagina, are favorite sites of infection. The vagina lined with pavement epithelium becomes infected, although less frequently than the urethra. In the young, the vaginal mucosa is more easily infected, because the epithelium is softer and more like columnar epithelium. This accounts for the frequency of vulvovaginitis in children.

The next situation most commonly involved is the cavity of the uterine cervix. The disease is very prone to become chronic here, just as in the glands of Bartholin and Skene.

The symptoms of gonococcal invasion of the genital organs in women may be severe or mild.

In severe cases, it is characterized by burning and smarting on urination. Within a few hours, the discharge appears at first mucoid, but soon becomes purulent. The pus, as in the male, may become greenish-yellow and mixed with blood. The onset of invasion may be ushered in by a chill, rapid pulse and an elevation of temperature.

More frequently, the symptoms of invasion are not pronounced. Usually there is smarting on urination and an increase of the vaginal discharge. Sometimes the only history one can obtain is that of an irritating leucorrhœal discharge. Sometimes the symptoms of invasion are so mild, that the first symptoms which the patient notices are due to vulvovaginal abscess, salpingitis or cervical inflammation.

In the chronic cases, the vaginal discharge although usually profuse, loses its purulent character. The symptoms will depend upon the sites of infection. These may be the urethra, cervix, tubes and peritoneum, or Skene's or Bartholin's glands.

Diagnosis of Gonorrhea in Women.—In the acute form the diagnosis is established by (1) history of suspicious intercourse, (2) clinical symptoms, (3) finding of the gonococcus in the discharges.

In subacute and chronic cases, the diagnosis is more difficult. It rests on a history of coitus, followed by frequent and painful urination and profuse vaginal discharge. Sometimes these are so mild or transient that they escape notice. Questioning the husband will sometimes elicit the statement that at some time prior to marriage he had gonorrhea.

The presence of the "maculae gonorrhoeica" of Sanger is strong presumptive evidence of gonorrhea. The redness persists for a long time after all active inflammation has ceased.

In examining a woman for gonococcal infection, it is important that she should come for examination without previous douching or cleansing of the genitals. She is placed in the dorsal position and examined in a good light. Smears are made from the discharge from the vulva and from the orifices of Skene's and Bartholin's glands.

The finger is then passed into the vagina with the palmar surface upward and the urethra is stroked from above, downward and forward, and any secretion that is expressed is collected on a slide. A speculum is next inserted into the vagina and a smear made from the cervical discharge.

Frequently, after a thorough examination, it is impossible to obtain bacteriological confirmation of the disease when the clinical evidence is strongly presumptive of its presence. It should be remembered that the gonococcus is most easily found just after the menstrual period. In doubtful cases, repeated examinations should be made at this time.

Treatment of Gonococcus Infection in Women.—In the acute stage, **rest in bed** and **strict cleanliness** should be insisted upon. The diet should be bland and free from spices and stimulants. **Water** should be freely drunk. The bowels are kept free by the frequent use of **saline purgatives**.

For frequent and painful urination, the **citrate of potash and bella-donna** mixture are given. **Sandalwood oil**, preferably in capsules, is also indicated.

The genitals are flushed, at least three times a day, with 1 per cent. **hot boric acid solution**. A sterile pad of soft absorbent gauze should be worn constantly over the vulva. When it becomes soiled, it is burned and a fresh one applied.

Local treatment is not begun until the acute inflammation has subsided. The number of drugs recommended for the local treatment is legion. The writers have obtained the best results with **argyrol** 20 per cent., **protargol** 2 per cent., and silver nitrate 1 to 10 per cent. The local treatment must be thorough and persistent. The patient, having emptied her bladder, is placed in the dorsal position in a good light. The vulva is cleansed with cotton sponges dipped in warm water and then wiped with dry cotton. If urethritis is present, $\frac{1}{2}$ ounce of 20 per cent. argyrol or 2 per cent. protargol is injected into the urethra through a

soft rubber catheter, the eye of which lies just within the meatus. This solution is retained until the next urination.

A Sims' speculum is next inserted into the vagina, which is thoroughly cleansed and wiped dry. Two per cent. **silver nitrate** is applied to the cervical canal with cotton wound around slender applicators. The vaginal fornices receive the same attention. A **vaginal suppository** containing 10 per cent. argyrol or 2 per cent. protargol is then inserted, after which a cotton tampon is introduced to retain the silver salt. At the end of 48 hours, the patient removes the tampon and takes a cleansing douche of warm water, just before the next treatment.

In the declining stages of the urethritis, silver nitrate is more efficacious than argyrol or protargol. Applications of 2 per cent. silver nitrate are made to the urethra through an endoscopic tube. The silver is next applied to the orifices of Skene's and Bartholin's glands. In sensitive patients, the pain may be lessened by first applying 5 per cent. **novocain**, **aposthesin** or **cocain** and waiting five minutes before applying the silver.

In chronic cases, where Skene's glands are the seat of chronic infection, they are injected with 1 per cent. silver nitrate, through a hypodermic needle, the point of which has been dulled. In obstinate cases, and where the openings of the ducts have become stenosed, it is necessary to lay them open. A fine probe is passed through the duct the full length of the glands, and the tissues are then divided over the probe. The gland is then **cauterized** with 10 per cent. silver nitrate or destroyed by **fulguration**. The glands of Bartholin, if involved, receive the same attention. If abscess of these glands forms, it should be opened and the interior cauterized.

The vagina sometimes becomes congested and sore after several local treatments have been given. When this occurs it is best to make several treatments with **tampons soaked in glycerin and ichthyol (12-1) or boroglycerid**.

In rebellious cases, Kelly recommends the use of **iodoform powder** dusted on dry elastic non-absorbent cotton tampons, so placed as to moderately balloon out the vagina. The packing is done every third day. The patient removes the tampons on the night of the second day and takes a **douche of permanganate of potash 1:1500**.

The treatment of gonococcal infections of the uterus, tubes, ovaries and peritoneum involves **surgical procedures** for the consideration of which the reader is referred to special works on this subject.

Determination of a Cure.—The question is often asked, whether gonorrhea can be cured in a woman. The consensus of opinion seems to be that when the infection is limited to the vulva and urethra and does not extend beyond the cervix, cure is possible after careful and persistent treatment. When the gonococcus invades the endometrium, and the uterine adnexa and adjacent peritoneum, practically all authorities are agreed that the possibilities of a cure are very uncertain indeed. Although many of these patients are apparently cured and discharged as such, experience has shown that relapses may occur.

Before discharging a case as tentatively cured repeated examinations, just after the menstrual period, must show:

- (1) Absence of profuse purulent vaginal discharge.
- (2) Absence of purulent discharge from Skene's and Bartholin's glands.
- (3) Absence of urethral discharge.
- (4) Negative smears and cultures.
- (5) Negative complement-fixation test.

GONORRHEAL VULVOVAGINITIS IN CHILDREN

Occurrence.—The prevalence of this infection among children is estimated in the various clinics as follows: Sara Welt-Kakels observed, in her clinic at Mount Sinai Hospital, 191 cases of vulvovaginitis during the ten years from 1893 to 1903, representing 1.6 per cent. of all the children treated. The largest number occurred between the ages of 2 and 5 years. After the tenth year the disease was rare. Dr. Flora Pollock, of the Johns Hopkins Hospital Dispensary, reports 139 cases in a series of 1,366 patients. Of these only three cases were congenital, the rest being acquired infections.

It is believed that adhesions of the labia and prepuce, occlusion of the hymen, diseased uterine tubes and deformed uteri are the sequelæ of this disease. The complications are acute peritonitis, arthritis and ophthalmia.

Etiology.—Soiled linen, infected towels or hands soiled with discharges from the mother or father infected with the disease, are the usual carriers of the infection.

Overcrowding and unhygienic surroundings predispose to its transference. Epidemics may occur in institutions, hospitals, asylums and nurseries, due either to ignorance of the nature of the discharge or carelessness in handling it.

Many individual cases are due to rape, due to a superstition among the lower classes that the disease can be cured by coitus with a healthy person, preferably a virgin.

Pathology.—The vagina and vulva are involved. The inflammation is most pronounced at the vaginal outlet, around the hymen, where the pus passes over the perineum.

Symptoms.—The incubation period is from 3 to 4 days. The child may complain of burning on urination and pain on walking, or the mother notes a discharge.

Locally, a profuse purulent discharge is seen pouring out of the vagina. The labia majora are usually reddened and swollen. Excoriations of the integument surrounding the vulva and on the inner sides of the thighs may be present. In cases due to rape, there may be considerable evidence of traumatism.

Diagnosis.—The disease must be differentiated from non-specific vulvovaginitis, due to uncleanness, urine or rectal worms. These

conditions occur most frequently in hot weather. Non-specific vulvovaginitis may occur in the course of measles and scarlet fever. The gonococcus is present in the discharges and its recognition establishes the diagnosis in specific cases.

Treatment.—The mother should be informed of the nature of the disease and of the danger of conveying it to other members of the family. Strict attention should be paid to **cleanliness**. All cloths and dressings should be sterilized by boiling, or should be burnt.

In the acute stage, where there is swelling of the vulva and profuse discharge, the child should be **kept in bed**.

The vulva is copiously flushed three times a day with either **hot boric acid** solution or **1-2000 potassium permanganate**.

If there is much vaginal involvement, irrigations of the vagina are advised, by some gynecologists, with the above-mentioned solutions. These can be given through a soft rubber catheter 12 Fr., gently inserted through the opening of the hymen, after the vulva has been thoroughly irrigated. Personally, we prefer the injection of about 4 to 6 c.c. of **20 per cent. argyrol** freshly prepared.

The degree of vaginal involvement may be determined by inserting a small endoscopic tube into the vagina, with the child in the knee-chest position. In this way the vagina can be examined and the cervix examined for discharge.

In infants, if, after wiping the vulva dry, pus continues to pour out when the child strains or cries, it denotes that the vagina is involved. After flushing the vulva, the parts should be gently dried and an absorbent dressing applied. To protect the skin from irritating discharges, an ointment is applied. **Zinc oxid** or a **3 per cent. protargol** ointment will be found useful.

From time to time, the discharge is examined for gonococci and active treatment continued until they disappear.

In the subsiding stages of the disease, the argyrol is replaced by **instillations of 1 per cent. silver nitrate**, administered three times a week. If erosions persist in the cervix or vagina, they may be touched up with silver nitrate 3 to 5 per cent., through an endoscopic tube or a Kelly No. X speculum. If the urethra is involved, it should be injected daily with **10 per cent. argyrol**.

Whatever the treatment, it should be persisted in until the discharges are free from gonococci. When this occurs, a complement-fixation test is performed. If negative, the case is discharged as tentatively cured.

As the disease has a tendency to recur, the child should be examined from time to time, during the year following.

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CHAPTER XVIII

RABIES

BY EUGENE R. WHITMORE, B. S., M.D., DR. P. H.

Definition, p. 521—Synonyms, p. 521—Etiology, p. 521—Epidemiology, p. 524—Mechanism of the disease process, p. 525—Symptomatology, p. 526—Diagnosis, p. 530—Treatment, p. 535—General prophylaxis, p. 534—Prophylactic treatment, p. 535—Treatment of the developed attack of rabies, p. 544—Prognosis, p. 545—Pathology, p. 545—History, p. 547—Geographical distribution, p. 548.

Definition.—Rabies is an acute infectious disease, transmitted by the bite of an infected animal, and characterized by a condition of increased nervous system excitement followed by paralysis.

Synonyms.—Hydrophobia; Lyssa.

Etiology.—In ancient times it was well known that rabies was transmitted by the bite of a rabid animal; and it was later shown that the virus was contained in the saliva. The virus was shown to be present in the salivary glands—especially the submaxillary glands—and in the central nervous system. This virus was studied by a large number of persons; and Pasteur developed the method of preventive inoculation before much was known about the virus.

The rabies virus belongs to a group of viruses which pass through bacterial filters, hence the designation "filterable virus." Some of these viruses are cell parasites, and the infected cell reacts by the production of a substance which appears in the cell: these are the viruses to which Prowazek gave the name "chlamydozoa"; that is, cloakbearing. Further, some of these viruses, when transmitted from the animal in which they commonly occur to another animal and carried through a number of passages in the animal, will not produce disease when inoculated back into the animal from which they came, but will produce immunity to infection in the natural way.

This last characteristic of the rabies virus gives the names of "street virus" and "fixed virus" as used by Pasteur.

Pasteur used the term "street virus" to designate the rabies virus that is transferred under natural conditions from dog to dog, from dog to man, or from dog to some other animal.

When this "street virus" is inoculated into rabbits, and is carried from rabbit to rabbit by subdural injection of material from the central nervous system, the virulence of the virus for the rabbit gradually increases, and the incubation time becomes shorter and finally becomes very nearly constant; that is, the "street virus" has become "fixed virus." Thus, "street virus" injected subdurally into a rabbit will kill the rabbit in about eighteen days; as the virus from this rabbit is injected into another rabbit, and so on, the incubation time gradually shortens, until the rabbit develops rabies regularly in eight days. This shortening of the incubation period means that the "fixed virus" pro-

duces a stronger toxin than does the "street virus," and, in keeping with this, the central nervous system becomes infectious in less time after inoculation with "fixed virus" than after inoculation with "street virus," indicating higher virulence in the "fixed virus."

There is some evidence that there are different strains of rabies virus. A street virus which Remlinger obtained from a fox, killed rabbits in nine days. The rabies virus in Dakar kills rabbits in fifteen to seventeen days and has been claimed not to produce rabies in man. Some tests of antirabic vaccination, carried on by Schoening at the United States Department of Agriculture, indicate that a vaccine prepared from one strain of rabies virus affords different degrees of protection against different strains of rabies virus. Several laboratories have noted variations in the original Pasteur strain of rabies virus as carried at different laboratories; but it has been pointed out that differences in the details of propagating the virus at different laboratories may account for the variations in the strain.

There is difference of opinion as to how the rabies virus becomes "fixed." Some authorities hold that it is the tissue into which the virus is injected that determines the fixing—fixed virus is a nerve tissue virus. Other authorities hold that it is the species of animal into which the virus is injected that determines the fixing. In the case of the smallpox virus, it seems to be the species of animal into which the virus is inoculated that brings about the modification of that virus.

For us, the great advantage of the "fixed virus," is that, when injected subcutaneously in suitable doses, it is not infectious for man, and it is far less infectious than "street virus" for dogs, monkeys and other animals; and, when so injected, it produces immunity against infection with "street virus." But the "fixed virus" is not innocuous when injected in large doses in man or dogs, as shown by the experimental production of rabies in dogs on injection of improperly treated virus, and as was shown by Boreggio's unfortunate experiences on injecting it into man. Various workers have tried to return "fixed virus" to "street virus"; but all attempts have failed, just as all attempts have failed to return smallpox vaccine virus to smallpox virus.

The year 1903 gave us important additions to our knowledge of the rabies virus; as Remlinger demonstrated the filtrability of the virus, and Negri discovered, in the pyramidal cells in the central nervous system, the bodies that bear his name.

Negri bodies are round or oval bodies, varying greatly in size, from one to twenty-seven microns in diameter—in the dog they are usually from four to ten microns in diameter. The number of these bodies in a nerve cell varies from one to five or six. The bodies are found in the ganglion cells in the central nervous system; so they are found wherever these cells are found. On account of the abundance of ganglion cells in the hippocampus (Ammon's horn), the Negri bodies are most numerous there; but they are also found in the Purkinje and pyramidal cells in the cerebellum, in the cerebral cortex, in all parts of the brain, and in the nerve cells in the spinal cord.

While Negri bodies are numerous and large in the central nervous system of animals dead of "street virus," they are much smaller and are not so numerous following inoculation of "fixed virus." Froesch has

suggested that the reason for this is that the shortening of the incubation period does not give time for the bodies to develop.

The Negri bodies are found in the central nervous system of animals infected with rabies; and they are never found in any other animals. By differential staining, the Negri body is seen to consist of one to twenty or thirty dots that stain deep blue or black with methylene blue, embedded in a hyaline matrix that stains magenta with eosin. In sections of the brain, the bodies are always intracellular, and contain the dots, known as "inner bodies." When examined in the fresh state, the Negri body appears as a homogeneous mass of ground substance, packed full of coccus-like granules.

While there is agreement that the Negri bodies are characteristic of rabies, there is difference of opinion as to what the bodies are. Negri was of the opinion that the bodies were protozoa; and some authorities hold that view, and consider the "inner bodies" to be granules of chromatin. Others hold that the Negri bodies are reaction products of the infected cell, and that the virus itself is not seen. Lentz describes the formation of the mass of ground substance from the substance of the infected cell. The third and most commonly held view is that the "inner bodies" are the virus, while the mass of ground substance is a reaction product from the infected cell. Koch considers the "inner bodies" to be the virus in the form of coccus-like bodies, and that the ganglion cells, being more resistant than the other cells, encapsulate the virus with a layer of degenerated cytoplasm.

In some early work, Pasteur noted numerous fine granulations in the central nervous system of animals dead of rabies; and he suggested that these granulations were the virus of rabies. Since that time, numerous workers have studied these granulations, without being able to determine what they are. These fine coccus-like points are found irregularly throughout the substance of the central nervous system, especially in the gray matter. They are also found in the salivary glands. Koch suggests that these coccus-like bodies are the virus of rabies.

Levaditi and his co-workers, Manouelian and Viala, and Caronia and Sindoni have recently discussed the nature of rabies virus; but they are not in agreement, and so do not seem to bring us any nearer to an understanding of the nature of the virus.

The rabies virus in the brain is protected from the action of physical and chemical agents; and this has led to a belief that the virus is unusually resistant to unfavorable influences. However, Poor and Steinhart have compared the virus from the brain with that from the salivary glands, filtered through a Berkefeld filter, and they conclude that the virus is actually more resistant than many known organisms. Galtier showed that the virus remained alive in the brain of a dog that had been buried forty-four days. At -4°C . (24.8°F .) it remains virulent as long as thirty-four months. The virus is rapidly reduced in virulence by air, light and drying; but there is difference of opinion as to whether this is simply an attenuation of the virus or actual killing of it, and in that way reducing the dose of the virus in a given amount of material. By Pasteur's method of drying the cord, the virus completely loses its virulence in ten to fifteen days. Harris has shown that freezing and drying in *vacuo* does not decrease the virulence of the virus to any extent. In *vacuo*, in the dark, the virus retains its virulence for thirty

days at a temperature of 23° C. (73.4° F.), and twenty days at 35° C. (95° F.). It is killed in one to four hours at 45° C. (113° F.), in one hour at 50° C. (122° F.) in half an hour at 52° to 58° C. (125.6 to 136.4° F.), and in five minutes at 60° C. (140° F.). The virus is not affected by 33 per cent. neutral glycerine in eighty days; and this is a satisfactory method of preserving the virus; the glycerine kills the contaminating bacteria, so such material can be used for inoculation of animals for diagnosis. Stronger solutions of glycerine kill the virus after twenty-five or thirty days. The Negri bodies are well preserved in the 33 per cent. glycerine solution. The virus is killed by chemical agents as follows: 1:1000 solution of bichloride of mercury, in two to three hours; 0.08 per cent. solution of formaldehyde, in two hours; and formaldehyde vapor in forty-five minutes.

Remlinger showed that the rabies virus diffuses through glycerine and even through normal tissues that have been immersed in glycerine containing rabies material; and, from that diffusibility, and its behavior on filtration, Remlinger suggests that the rabies virus may be considered as intermediate between the smallest visible organisms and the enzymes. Imamura and Ando were not able to confirm the diffusibility of the rabies virus into glycerine or other fluids. The rabies virus passes through the placenta, from the mother to the foetus, as has been shown in the cases of human, sheep, rabbit and guinea pig.

Various attempts at cultivation of the rabies virus have been made, and some successful cultivations have been reported; but none of the cultures have been carried beyond the stage of purely scientific interest.

The rabies virus produces a toxin which seems to be partly bound to the nerve tissue. Rabies material filtered through a Chamberland filter produces emaciation, paralysis, and death in experimental animals; but, the central nervous system of these animals is not infectious. Galtier found that the rabies toxin was capable of producing paralysis, even after heating to 100° to 105° C. (212° to 221° F.).

Epidemiology.—Rabies in man and lower animals is the result of inoculation of the virus through the bite of rabid animals; and the dog is peculiarly adapted to spread the infection. The disease occurs among all warm blooded animals; but the dog and cat families are the ones most commonly affected. Some birds are occasionally infected with rabies, but these do not play any part in the spread of the infection.

(a) **SOURCE OF INFECTION.**—From its habits, the dog is the common transmitter of rabies to other animals and especially to man. This results from the condition that the dog comes and goes as it pleases, and comes in close contact with man. The long teeth of the dog, making a deep or torn wound, make infection more common after dog bites. In some frontier regions, the wolf plays a part in the spread of rabies; and the fox may also transmit the infection. In India, jackals are quite frequently infected; and they transmit the infection to dogs, and not infrequently to man. Of 569 persons treated at the Pasteur Institute at Shillong (Assam) in 1917, 97 had been bitten by rabid jackals. Coyotes and skunks are frequently infected in the western part of the United States; and they transmit the infection to dogs and not infrequently to man. Cats are rather frequently infected, though the disease in them is apt to be of the paralytic type. Of 7,594 animals examined for suspected rabies at the Vaccine Division of the Institute of Experimental Medicine, in

Petrograd, from 1912 to 1921 inclusive, 7,157 were dogs (of which 2,119 were rabid); 346 were cats (of which 128 were rabid); and only 91 were other animals. In Washington, D. C., in 1925, a pet cat became rabid and bit five persons. Cattle are rather frequently infected, as are horses; but these animals do not so readily transmit the infection to man, partly because they do not come in such close contact with him, and partly because their teeth crush rather than puncture or tear when they bite. Oushakoff reports from all Russian antirabic stations, 2,859 persons bitten by suspected rabid horses, and 3,522 persons bitten by suspected rabid cattle: one person bitten by a horse died of rabies; no person bitten by a cow developed rabies.

Goats, sheep and pigs are not infrequently infected, and they may transmit the infection to man. Rats and mice are also often infected; but it does not appear that they play much part in the spread of rabies or in the infection of man. During the summer of 1925, I treated here in Washington, two persons who were bitten by a rabid rat. Prairie dogs are not infrequently infected. Schmitter observed a case of rabies in a wild monkey in the Philippines.

So, for practical purposes, it may be considered that the dog is the animal responsible for the spread of rabies, as is indicated by the eradication of the disease from England and the prevention of its entrance into Australia as a result of preventive measures directed against the dog as the transmitter. Also, the dog is far the most important transmitter of the disease to man, as is shown by Dobert's tabulation of rabies in Prussia. From 1903 to 1907, 1,069 rabid animals injured, mostly by bites, 1,817 persons; 1,025 (94.1 per cent.) of these animals were dogs; 37 (3.4 per cent.) were cats; 15 (1.4 per cent.) were cattle; 6 (0.6 per cent.) were horses; 4 (0.4 per cent.) were hogs; and 1 (0.1 per cent.) sheep. There is only one case reported in which it seems practically certain that the infection was transmitted from person to person; though naturally, a number of persons have received some minor wound, or have gotten the patient's saliva on their skin, while caring for cases.

(b) MODE OF TRANSMISSION.—There is no evidence of the transmission of rabies in any other way than through the saliva of the infected animal—generally by a bite; at times by the rabid animal licking the hand of a person, the virus being licked into some abrasion on the skin. Slight abrasions may suffice for the inoculation of the virus; and it is not necessary that the bite be deep. There is no proof that the infection is transmitted by meat or milk from infected animals; and Roehaix and Papacostas have shown that the virus will not pass through the unbroken intestinal mucosa. There is no proof of its transmission by coitus. Remlinger could not produce rabies in guinea pigs by instillation of an emulsion of a highly virulent virus into the conjunctival sac; but he succeeded in producing rabies in about one of four or five attempts by instilling a small amount of an emulsion of the virus into the nasal cavity, taking care not to injure the mucosa.

The saliva of an animal may be infective as long as three to five days—even seven days—before symptoms develop. On the other hand, it is often difficult to demonstrate the infectivity of the saliva even after the symptoms of rabies have developed. In D'Aunoy's case of recovery from rabies in a rabbit, the saliva was infective nine days after development of symptoms, but not forty days after development of symptoms.

(c) **SUSCEPTIBILITY.**—Susceptibility to rabies varies in different animals. In the lower animals it is usually considered that 40 to 70 per cent. are susceptible, while man is much less susceptible. Thus, some authorities put the susceptibility of man as low as 5 per cent., while others put it as high as 50 per cent. The danger of infection varies with the number and the severity of the bites. Multiple bites and deep lacerated bites are more likely to transmit the infection than are the crushing bites of horses and cattle. There is more danger of infection when the virus is inoculated by a bite on the uncovered skin than when through the clothing. Subcutaneous injection of the virus produces rabies in about 50 per cent. of experimental animals; and Remlinger says that with a virus of high virulence for the guinea pig, subcutaneous inoculations frequently fail.

While it is generally considered that rabies is more common in the summer months, statistics of the disease in Germany do not bear out that belief. Bigelow and Webber's tabulation of cases of rabies by month, does not show any marked excess in the summer months; and in Seattle, an outbreak of rabies began in September, 1913, and there were 361 cases of canine rabies in the city to June, 1914. Sellers says that any apparent difference in the summer and winter months is due to the cold weather preventing animals, as dogs, making such long excursions and so there is not such marked mixing of the animals in winter.

Children are more susceptible to rabies than are adults. There is no difference in sex susceptibility. Children from six to fifteen years old are more commonly bitten, and boys are more commonly bitten than are girls: this seems to be dependent entirely on the habits of children playing in the streets and fields and making no effort to avoid a strange dog.

Symptomatology.—(A) **RABIES IN LOWER ANIMALS.**—The clinical picture of rabies is in general the same in all susceptible animals; and, since the dog is the lower animal in which the diagnosis has usually to be made, it is best to discuss the symptoms of the disease in the dog. While the symptoms may vary somewhat, as a result of age, sex, race, and temperament, it is possible to distinguish two varieties: the furious rabies and the dumb or paralytic rabies; and each variety is marked by three stages: the prodromal stage, the stage of excitement and the stage of paralysis.

INCUBATION PERIOD.—The incubation period varies greatly; being on the average from five to eight weeks in natural infections. Haubner gives the incubation period as less than two months in 83 per cent. of his cases, within three months in 16 per cent., and in the fourth month or later in the remaining one per cent.

In experimental rabies the incubation period is shorter, partly because a larger dose of virus is injected than in the natural infection, and partly because the virus is in a more concentrated form and is injected directly into the central nervous system. The average incubation period, when the street virus is injected into the muscles of the lumbar region, is about seventeen days; when the virus is injected subdurally, it is from ten to fifteen days. Konradi reports one case where a rabbit died of rabies thirteen months after subdural inoculation of brain emulsion of a child dead of rabies.

I. *Furious Rabies*.—In the *prodromal stage* the dog shows a change in disposition: a good-natured, playful dog appears dejected, and slinks away into a dark place. In other cases, the dog is unusually friendly, and even a vicious dog may be friendly; in such a case the dog may show a disposition to lick his master's hand; and, as the saliva is already infectious, there is danger of infection through any cuts or abrasions on the skin of the hands. At times the dog may act normal, or be unusually active; and this state may alternate with periods of dejection and slinking. The animal may start at any sudden noise. The site of the bite is often irritated, and the dog may lick it.

An important thing in this stage is the abnormal appetite: the dog does not care to eat its food, but will swallow all sorts of material as sticks, stones, hair, leather and dirt. This must be kept in mind in the post-mortem examination of a dog suspected of having rabies.

The *stage of excitement* is the period that gives the name of "mad dog" to the rabid dog. One of the most important signs is that a dog which is never in the habit of leaving home will run away; and the dog may travel miles, never getting back home, or returning worn out with running and with its coat full of dirt and its flesh torn from fighting with other dogs. Many times the dog snaps at and bites everything it comes near; and such a dog may run among a group of persons and bite a number of them before it runs on in its mad rush over the world.

Corwin tabulates the number of miles traveled and the number of dogs known to have been bitten by eight rabid dogs in Connecticut: the greatest distance traveled by one rabid dog was forty miles, with an average of eighteen miles; the greatest number of dogs known to have been bitten by one rabid dog was twenty-seven, with an average of twelve.

A change in the bark is said to be characteristic: the bark changes to a hoarse howl.

After two to four days, the dog develops weakness in the hind legs and hips and passes into the *paralytic stage*. The dog appears weak, staggers as it walks, and may fall. This weakness may extend to the front legs, and to the muscles of the jaw. At times the jaw is affected first: the lower jaw hangs down, and bloody froth flows from the mouth; the dog cannot bite, and raises the head with difficulty. There is great emaciation, with profound weakness, and death follows.

Duration.—The prodromal stage lasts about one or two days; the stage of excitement two to four days; and the paralytic stage one to two days. The entire course of the disease, after symptoms appear, is usually five or six days; never more than ten days.

II. *Dumb or Paralytic Rabies*.—In this form of rabies, the *prodromal stage* and the *stage of excitement* are short, and may be overshadowed by the *paralytic symptoms* from the start. There is often increased excitability, but the weakness makes it impossible for the dog to run, and there is not the furious running through the country, such as is seen in the stage of excitement in the furious type of rabies. The weakness may begin in the jaw; and "jaw drop" may be one of the first things noted. The weakness rapidly spreads to the body, and the dog is soon not able to walk or stand. It lies quietly, the body being shaken from time to time with short muscular cramps.

It would appear that paralytic rabies is merely a severe form of

rabies, as it is common in experimental rabies when the inoculation is into the muscles, and it is the form that is seen in the rabbit following inoculation of fixed virus. But at times dogs with paralytic rabies live longer than do dogs with furious rabies; though it may well be that the average duration of paralytic rabies is shorter than the average duration of furious rabies.

Under natural conditions, about 80 to 85 per cent. of dogs develop furious rabies, and about 15 to 20 per cent. develop paralytic rabies.

(B) RABIES IN MAN.—The forms and stages of rabies in man are the same as those in the dog, except that the furious form is represented by a spasmodic form.

Incubation Period.—The incubation period varies even more in man than it does in the dog. The minimum incubation period observed is twelve days. Kozewaleff observed 212 cases of rabies in man; the incubation period was twenty to forty days in 40.6 per cent. of the cases; forty to sixty days in 25 per cent. of the cases; twelve to twenty days in 13.7 per cent.: that is, the incubation period was less than sixty days in 79.3 per cent. and over sixty days in 20.7 per cent. The incubation period was over two hundred days in 3.8 per cent. of the cases; over a year in three cases and over two years in one case. Koch says that the rabies virus may lie dormant in the nervous system for a long time, and be roused by trauma, fatigue, emotional stress or abuse of alcohol.

The long incubation period and the great variation in the length of the period in man probably depends on several factors. One of the most important seems to be that man is not very highly susceptible to the rabies virus. Other factors are virulence of the virus; the depth, size, number and location of the bites; and the age of the patient—children are more susceptible than are adults.

Ordinarily there are no symptoms during the incubation period; though there may be some anxiety, probably due to fear of the development of rabies.

I. *Spasmodic Rabies.*—Rabies in man does not take the furious form that is so common in dogs; but rather takes a spasmodic form, such as is not infrequently seen in guinea pigs in experimental rabies.

In the prodromal stage, there is often irritation in the scar of the bite; this irritation amounting to itching or pain, with redness or edema. There may be neuralgic pains in various parts of the body. The patient has headache, and there is loss of appetite. The important symptoms are psychic in nature: the patient is depressed and anxious, and cannot sleep. The voice is often changed, especially in children, to a peculiar whine.

At times the stage of excitement sets in suddenly, without any prodromata. More commonly it is preceded by prodromata. The first characteristic symptom is the spasm of the muscles of deglutition, making it difficult or impossible to drink water, and giving the feeling of something in the throat. This spasm of the muscles of deglutition is a prominent feature throughout the course of the disease; and the patient early develops a fear of trying to drink, on account of the painful spasms in the throat—hence, the name “hydrophobia.” But the fear of water may be absent throughout the disease. The irritability increases until the slightest stimulus, as the sight or mention of water, a draft of air, a noise, a bright light or even a touch, brings on the severe spasm of the muscles

of deglutition. Spasm of the muscles of respiration comes on early; and there is precordial distress. The special senses are hyperæsthetic.

These spasms come on in the form of attacks, which do not last more than half to three-quarters of an hour. An attack is often induced by the slightest irritation. Beginning with spasm of the muscles of deglutition, the spasm spreads to include certain groups of muscles, as those of respiration, or there may be generalized convulsions. These convulsions may be mild or severe, being even tetanic in character. It is possible to see the spasm of the muscles in the throat; and a little saliva or mucus is frequently expelled from the lips as a result of this spasm. The peculiar sound that has been likened to the barking of a dog is due to spasm of the muscles of the larynx. There is dyspnoea; and the patient may die in one of these attacks. The spasm of the muscles, extending to the muscles of the jaw, gives rise to the peculiar chewing or snapping movements that have been considered to resemble the biting movements of the rabid dog. The abundant salivary secretion may be churned to a froth by the spasm of the jaw muscles. There is great anxiety, which may be increased to a sort of mania, with delusions and hallucinations. In this condition, the patient shudders, springs from his bed, and rushes to the door and about the room; clutches at his throat; gets on all fours and grovels on the floor; and, when restrained, begs to be allowed to go.

Between attacks, the patient is quiet, and his mind is clear; though there is great anxiety. Even during the attacks, the patient is conscious, and tries to avoid injury to those who are caring for him. Allen and Horne report a case where a child with rabies bit her father on the hand; but it is not clear whether or not it was an accidental bite as a result of the father trying to relieve the child's suffering during one of the spasmodic attacks.

There is fever of 100° to 107° F. (38° to 42° C.); and high terminal temperature, such as is met with in a number of other conditions (as delirium tremens) may occur. Nausea and vomiting are common; the vomitus frequently being blood stained. In the beginning, the pulse is full and bounding, but later it becomes weak and rapid, especially during the spasmodic attacks. The urine is decreased in amount, and does not contain albumin; but it may contain sugar.

The patient may die suddenly in a convulsion or from asphyxia, during one of the spasmodic attacks; or the attacks may become more frequent, and the patient die from exhaustion. More commonly, when the patient does not die during one of the attacks, he passes into the paralytic stage; the spasms stop, and there is great weakness and paralysis. The cessation of the spasms makes it possible for the patient to drink water, and the respiration is quiet; so there may be an appearance of improvement. But the paralysis increases, and the patient passes into coma and dies.

Duration.—The prodromal stage may last three or four days, or it may be entirely absent; and the feeling of something in the throat and the inability to drink may be the first signs of the disease. Death does not occur in the prodromal stage.

The stage of excitement lasts from one to four days; usually two or three days. Death is frequent in this stage from apoplexy; in a convulsion; or from asphyxia, suddenly, or after a short period of agony.

The paralytic stage does not last over two to eighteen hours, and death is in coma.

The average duration of the disease, from the time the spasms of the throat set in, is two to three days.

II. *Paralytic or Dumb Rabies*.—Just as with the dog, the prodromal stage and the stage of excitement may be very short, and the paralytic symptoms predominate from the start. Children and persons severely bitten, as by wolves, seem more liable to develop paralytic rabies.

Diagnosis.—The mortality in human rabies is 100 per cent., but it is possible to prevent development of rabies in man in over 95 per cent. of the cases by prophylactic inoculation after the person is bitten. This indicates the great importance of prompt diagnosis of rabies in animals; the dog being the animal that is all-important in transmission of rabies in man.

CLINICAL DIAGNOSIS OF RABIES IN DOG.—A clinical diagnosis of rabies in the dog is practically impossible, owing to other conditions that may simulate rabies. The history of the dog is important. One of the most important signs is that a good-natured, playful dog becomes cross, and slinks away into a dark place; or a cross dog becomes affectionate. The dog may leave home and travel for miles; then return home, emaciated, tired and torn from fighting. In the nature of things, it is difficult to find evidence that a dog was bitten by some other animal.

When a dog is suspected of being rabid, it should not be killed, but should be shut up and observed for ten days. If, at the end of that time, the dog remains well, it may be considered that the dog was not rabid.

LABORATORY DIAGNOSIS OF RABIES IN DOG.—When a suspected rabid dog dies or is killed, the brain should be examined, since a laboratory diagnosis is the only way in which a satisfactory diagnosis can be made. In killing the dog, care should be taken not to crush or shatter the brain, as this leads to rapid contamination with bacteria and the brain will very soon be unsuited for animal tests. If the examination has to be made at a laboratory that is some distance away, the dog's head should be cut off and sent to the laboratory, packed in ice. If it is necessary to send the head some distance for examination, and it is not possible to pack it in ice, the brain may be removed carefully and sent in 33 per cent. glycerine solution in water; or it may be packed in borax.

I. *Stomach Findings*.—In the examination of a dog for rabies, it is very important to examine the stomach and its contents. If the dog's stomach contains normal stomach contents, and the small intestine contains normal intestinal contents, the probability is that the dog did not have rabies. On the other hand, if the dog's stomach contains sticks, stones, leather and other indigestible matter, it is probable that the dog had rabies. It is necessary to be careful not to make a diagnosis of rabies on the finding of foreign substances in the stomach, as it is not uncommon for dogs to have masses of foreign matter—especially hair—in the stomach. In one case of suspected rabies in a pup, a mass of excelsior was found in the esophagus at post-mortem, and it was difficult to say whether it was the result of the perverted appetite of a rabid dog or an accident to a playful pup. It is also necessary to be very careful in interpreting the appearance of submucous hemorrhages in the stomach.

II. *Microscopical Examination of Brain*.—(a) *Direct Examination for Negri Bodies*.—In examining a brain for rabies, a direct microscopical examination for Negri bodies should be made. If the information

obtained from this direct examination is not satisfactory, animals should be inoculated with the brain substance. At the same time some of the brain tissue should be preserved in neutral glycerine in the ice-box, for further animal inoculations in case of accident to the first set of animals. Possibility of accident must be guarded against in every way, in cases where the dog has bitten some person, as every day lost in making a diagnosis increases the patient's danger of contracting rabies in case the dog was rabid.

The brain is carefully removed from the skull, and parts of it taken for examination for Negri bodies. As the Negri bodies are in the large ganglion cells, it is necessary to take parts of the brain in which these cells are most numerous. For this reason the hippocampus major (Ammon's horn) is usually taken; though Negri bodies can be found in the pyramidal cells in the cerebral cortex and in the Purkinje cells in the cerebellar cortex. There is less danger of confusion from other cell inclusions when material is taken from the hippocampus or from the cerebral cortex for examination. Smears of the brain substance are examined, and if the information is not satisfactory, sections are cut and examined. If this examination does not give satisfactory information, some of the brain substance should be injected into rabbits or guinea pigs.

There are numerous methods of staining smears and sections for Negri bodies, and any of the methods will give satisfactory results. The Lentz method is preferred for diagnosis, as it gives clear-cut differential staining of the Negri bodies; and it is also possible to prepare stained sections in less than three hours by this method.

Technic of Lentz Method of Staining.—A thin transverse slice of tissue through the hippocampus is spread between two slides by gentle pressure and drawing apart of the slides. Without allowing them to dry, the slides are placed in methyl alcohol for ten minutes, and are then washed in a mixture of absolute alcohol and ether. For sections, a transverse slice of the hippocampus, not over 2 mm. in thickness, is placed in acetone in the incubator at 37° C. for one hour, then in paraffine in the 54° C. incubator for one hour; embedded and thin sections cut.

For the staining, five solutions are used: (1) A 0.5 per cent. solution of water-soluble eosin in 60 per cent. alcohol; (2) Loeffler's methylene blue solution; (3) Lugol's iodine solution; (4) five drops of a one per cent. solution of sodium hydroxide in absolute alcohol added to 30 ml. of absolute alcohol; and (5) one drop of 50 per cent. acetic acid solution added to 30 ml. of absolute alcohol. All of the solutions keep well, but the alkaline alcohol must be free from water.

Stain in the eosin solution for one minute; wash in water; stain in Loeffler's methylene blue one minute; wash in water; mordant with Lugol's solution one minute; wash in water; differentiate in methyl alcohol until the specimen is red; wash in water; stain with Loeffler's methylene blue, one-half minute; wash in water; blot dry with filter paper; differentiate in alkaline alcohol until only a faint tinge of eosin is left; differentiate in acid alcohol until only the ganglion cells appear faint blue under the microscope, the background of the specimen appearing faint pink; wash quickly in absolute alcohol. Smears are examined direct with oil immersion lens; sections are carried through xylol and mounted in balsam.

The Negri bodies appear crimson in the pale blue cytoplasm of the

ganglion cells, the inner bodies being stained dark blue to black. The red blood cells are stained vermillion and cannot be mistaken for Negri bodies.

Williams' Method of Staining.—Williams makes smears from the cerebral cortex, Ammon's horn and the cerebellum. The partly or completely air-dried smears are fixed for about ten seconds in methyl alcohol (that has been neutralized by the addition of about 0.25 gram of sodium carbonate to 500 ml. of the alcohol) with 0.1 per cent. acetic acid. The staining solution is 0.5 part of saturated alcoholic solution of basic fuchsin and 10 parts of saturated alcoholic solution of methylene blue, in 30 parts of distilled water. The staining solution is kept in the ice-box, as it deteriorates rapidly at room temperature. The stain is poured on the smear and held over the flame until it steams. The smear is then washed in tap water and blotted with filter paper. The Negri bodies appear magenta color, the nerve cells blue, and the red blood cells yellow or salmon color.

Heidenhain's Hematoxylin Stain.—While Lentz's method is satisfactory for diagnosis, it is not suited for study of the finer structure and for demonstration of the coccus-like granules in the central nervous system and in the salivary glands. The material is fixed in sublimate alcohol, and is stained with Heidenhain's hematoxylin with a light counter stain of eosin. The coccus-like granules appear as black points surrounded by a narrow zone, scattered through the tissue in regular groups.

(b) *Inoculation Tests with Brain Emulsion.*—If the examination for Negri bodies does not give satisfactory information, some of the brain tissue (preferably medulla oblongata) is emulsified in physiological salt solution and injected into animals. Rabbits are commonly used, though a number of laboratories use guinea pigs. The latter are more susceptible to rabies than are rabbits, and the incubation period is shorter. Drawbacks to the use of guinea pigs are that the disease is irregular in the pig, and not infrequently the pig dies in a few hours from the time it shows symptoms; so a second passage may be necessary to insure a diagnosis. The disease is regular in rabbits. Remlinger advises the inoculation of a pig and a rabbit with the brain emulsion; or the inoculation of a pig, and when the pig dies, the inoculation of a rabbit from it. A number of laboratories recommend the rat for diagnosis of rabies, on account of its greater resistance to infection with contaminating bacteria which may be present in the suspected material, and also because it is less likely than the rabbit to die to intercurrent disease.

If the brain tissue being examined is fresh and free from contamination, it is best to inject subdurally or intracerebrally, through a small trephine opening. Lapponi inoculates intraspinally, as he finds the incubation period is shorter than after subdural inoculation, and there is no danger of the inoculated material leaking out through the needle wound. If the brain is contaminated, it is necessary to inject it into the muscles of the back, or even subcutaneously, as subdural injection would kill the animal. Guinea pigs may be inoculated in the muscles at the nape of the neck or the thigh. The incubation period in the rabbit is twelve to twenty-one days, though it may be four to six weeks; and experimental animals should be kept under observation for two months. The incubation period is commonly under twenty days in the guinea pig.

Subdural, intracerebral or intraspinal inoculation is the best, as it

gives 100 per cent. of positive results; injection into the muscles on both sides of the spinal column gives 95 per cent. of positive results, while subcutaneous injection gives only about 50 per cent. of positive results.

In rabbits, rabies is usually of the paralytic form, though there are convulsions at times. Furious rabies is rare in rabbits, but it does occur. Street virus usually causes paralytic rabies in the guinea pig. The animal dies in two to four days after the beginning of symptoms: and the brain is examined for Negri bodies, as was the dog's brain in the beginning.

It is generally considered that production of a disease typical of rabies, by the injection of emulsion of brain, is sufficient evidence on which to base a diagnosis of rabies. However, search should always be made for Negri bodies in the brain of the experimental animals. Several observers have reported diseases which resembled rabies, but which could not be identified as rabies. The "Pesta de coçar" or "Molestia de Aujeszky" reported by Carini and Maciel, appears to be a specific disease which, if not rabies, does not deserve to be called pseudo-rabies.

Diagnosis in Man.—In man, the diagnosis of rabies must be made from the history and the clinical picture. A history of being bitten by a dog a month or two before—especially if a stray dog—together with irritation at the site of the bite, is strong indication of rabies. But one must be on guard against lycsophobia: in the latter case the stigmata of hysteria are present. Tetanus, delirium tremens and drug poisoning need only to be kept in mind to differentiate. Rabies is not uncommonly very irregular in man, and the disease may be confused with poliomyelitis or meningitis. The syndrome of Landry's paralysis should always make one think of rabies. The paralysis of the antirabic treatment are of the type of Landry's paralysis. There is an early leucocytosis in rabies. Negri bodies are found in the brain of man in about 40 per cent. of the cases, so it is frequently necessary to inoculate animals to make the diagnosis.

Treatment.—GENERAL PROPHYLAXIS.—More than 90 per cent. of all cases of rabies in the human are due to dog bites; and the disease is kept in existence by the canine family. For this reason, measures directed against the *source of infection* are primarily directed against rabies in the dog. Muzzling of dogs, destruction of stray and homeless dogs, and a high dog tax are the measures to be enforced.

In the Department of the Seine, the measures for the control of rabies consist of a dog tax and destruction of all stray dogs. By these measures the amount of canine rabies was greatly reduced, and rabies in man ceased to exist. But after the beginning of the World War there was some increase in the number of persons applying for Pasteur treatment, possibly as a result of difficulty in maintaining a strict enforcement of the measures for control of dogs; but since 1921 the number has fallen off until it is now about the pre-war figure.

In England, rabies has been eradicated by strict enforcement of the order for muzzling dogs. Before 1890, the number of cases of human rabies increased to such an extent that muzzling of dogs was enforced: the result being that the number of cases fell markedly in the next three years. As a result of opposition to muzzling, the order was not so strictly enforced in the next three years, with the result that at the end of that three years the number of cases of human rabies had increased

to twice what it has been before the period of muzzling. Muzzling was again enforced, with the result that the number of cases of human rabies decreased markedly until in 1900 there were no cases of human rabies in England. After an absence of about twenty years, rabies reappeared in England, as a result of evasion of the quarantine regulations during the war; but prompt and energetic enforcement of the muzzling regulation has again wiped rabies out in England.

In regions where wolves, jackals, coyotes, foxes and skunks play a part in the spread of the infection, special efforts at their destruction are necessary. The 1919-1920 report of the Nevada State Rabies Commission shows that an active war on predatory animals has led to a marked reduction in the number of cases of rabies in the state.

PROPHYLACTIC VACCINATION OF DOGS.—Since antirabic vaccination protects dogs as well as humans against rabies, it has been the practice for some years for persons to have valuable dogs protected by vaccination.

With the increase in rabies throughout the world, following the World War, attention was turned to antirabic vaccination of dogs as a method of preventing the spread of rabies in dogs and so to man. In Japan, the method has been carried out rather extensively and the results are decidedly good. In Tokio, about one-half of the dogs were vaccinated in the years 1919 to 1922. Of the vaccinated dogs, 31 developed rabies within a year after vaccination (fifteen of them in four to forty days after vaccination), while there were 1,323 cases of rabies among the unvaccinated dogs in the same four years. The results in Yokohama in the years 1918 to 1922 were as good as were the results in Tokio.

Antirabic vaccination of dogs, as a public health measure, has been in use in some parts of the United States for several years, and the results have been good. In Connecticut and Massachusetts, vaccination of dogs, is recommended, but is not required; while at least two municipalities in New Jersey have made antirabic vaccination of dogs compulsory in the past two years.

The Japanese method of vaccination of dogs was introduced into the United States by Eichhorn and Lyon in 1921 and has been used rather extensively here. The Japanese method consists of a single dose of vaccine divided into two injections under the skin of the shoulder and the neck. The vaccine is also available in the form of the Högyes dilution method, consisting of six doses given in six days. The results from both methods have been entirely satisfactory.

It is unfortunate that some people actively oppose the enforcement of muzzling regulations; and members of some of the societies for the prevention of cruelty to animals have carried on active propaganda against the vaccination of dogs. With a better understanding of the dangers of rabies, it is to be hoped that many of the opponents will change to supporters of these methods of prevention.

Since cats are frequently infected with rabies—as well as being great destroyers of bird life—it is important that stray and homeless cats be destroyed just as are dogs.

PERSONAL PROPHYLAXIS.—It is important to avoid being bitten by, or having abrasions soiled by the saliva of, rabid animals. If necessary to work with a rabid animal or to make a post-mortem examination of an animal dead of rabies, it is necessary to wear gloves and to see that there are no abrasions on the skin. Attendants on cases of human rabies should wear gloves and should see that they have no skin abrasions.

Since rabies has a morality of 100 per cent. in man, it becomes of the greatest importance to prevent the disease. When a person is bitten by a dog, it is necessary to consider the possibility of rabies and to treat the person according to whether or not the dog is rabid. The fundamental principle is that, unless it is possible to satisfactorily determine that the dog was not rabid, the person should be treated as though the dog was rabid.

PROPHYLACTIC TREATMENT IN MAN.—Prophylactic treatment consists of local treatment of the wound and general treatment in the form of immunization against rabies. The wound is always to be treated as though the dog was rabid—unless it is immediately evident that the dog was not rabid—since it is not possible to wait until the condition of the dog is determined before treating the wound. The wound is to be opened freely to the bottom and all shreds of torn tissue trimmed away, and thoroughly cleaned with an antiseptic solution. The wound should be encouraged to bleed. Of great importance is a thorough cauterization with nitric acid, which seems to have a specific action on the rabies virus. It has been shown that it is possible to prevent rabies in about 40 per cent. of experimental animals by applying a tourniquet above the wound and cauterizing the wound with nitric acid. Cumming, on the basis of the specific action of formaldehyde on the rabies virus experimentally, recommends that the wound be treated with formaldehyde. The efficiency of nitric acid and formaldehyde in destroying the rabies virus must outweigh the objection to their use on account of the pain produced by them. A simple dressing should be applied.

History of the Dog.—Whether the bitten person shall be immunized must depend on the determining of whether the dog was rabid; and the history of the dog and the conditions under which it bit are of great importance in determining this. If the person was accidentally bitten when playing with the dog, or was bitten when teasing the dog, or was bitten by a known vicious dog, it is not necessary to begin immunization; but the dog must be kept under observation for ten days. On the other hand, if the person was bitten by a stray dog that ran up and bit without provocation and ran on, or by a known dog that shows signs of being sick and especially, becomes cross, it is necessary to consider beginning immunization at once.

A couple of examples will illustrate how the history may or may not be of value in determining whether the dog was rabid. A stray dog ran among a group of soldiers, snapping right and left, and bit five of the men; then it ran on and began jumping and biting at the noses of a team of horses until the driver got down from the wagon and killed the dog. Under such conditions, the men should have been immunized at once; but the virus was not available, and one man died of rabies a month or two later. In another case, an old dog that had been a house dog and a pet for years was taken sick, without any signs of change of disposition, and without any definite signs as to what was the trouble, except that there was trouble in swallowing. The owner, who was a physician and familiar with rabies in the ordinary form, called a veterinarian; and the veterinarian repeatedly placed his hand in the dog's mouth to examine for anything there might be in the throat. The dog never showed any signs of snapping or biting, and the children cared for the dog until its death. Negri bodies were found in the brain of the

dog; and animals inoculated with brain substance of the dog, developed rabies. On finding the Negri bodies, the children were immunized; but the veterinarian decided not to be immunized. No one developed rabies.

Indications for Antirabic Vaccination.—It is necessary to carry out antirabic vaccination in every case where there is a chance that the person has been inoculated with rabies virus. At the same time it is desirable not to submit the person to treatment unnecessarily. On this account, different workers have formulated lists of *Indications for Antirabic Vaccination*. Heller and Rothermundt give the following indications, with a table from Marie and Remlinger.

1. If a man is (*a*) bitten by a dog, (*b*) has the uncovered skin soiled with froth or saliva, or (*c*) is scratched by the dog, it is not necessary to give antirabic vaccination if the dog is known, or is observed promptly and shows no disturbance, provided it is known that there has been no rabies in the region for six months. If there is rabies in the district, it is advisable to start antirabic vaccination at once, and to continue it until the dog can be observed for ten days.

2. All other cases are handled as follows:

- | | | |
|---|---|--|
| <ol style="list-style-type: none"> 1. If the dog dies in less than ten days after biting the man. 2. If the dog is killed in less than ten days after biting the man. 3. If the dog disappears. 4. If the dog is unknown. | } | Antirabic vaccination should be carried out. |
| | | |
| <ol style="list-style-type: none"> 1. Develops rabies. 2. Dies under suspicious circumstances. | } | Antirabic vaccination should be carried out. |
| | | |
| <ol style="list-style-type: none"> 5. If the dog is living and is observed for ten days. | } | <ol style="list-style-type: none"> 3. Is sick, but lives over ten days. <p>The dog should be observed further, and antirabic vaccination carried out if it develops rabies.</p> |
| | | |
| <ol style="list-style-type: none"> 4. Remains well at the end of the ten days' observation. | } | Antirabic vaccination should not be carried out. |

In all cases where the dog is killed or dies under suspicious circumstances, it is important to have the brain examined for Negri bodies, and to have animal inoculations carried out in case the microscopic examination of the brain does not furnish satisfactory information.

Development and Methods of Antirabic Vaccination.—In 1881 Galtier immunized sheep against rabies by giving them intravenous injections of the saliva of rabid dogs. But Pasteur's work placed antirabic vaccination on a practical basis. Based on the results in smallpox

vaccination, Pasteur considered it possible to attenuate the virus of rabies, and to produce immunity with that attenuated virus. His first experiments were carried out by passing the virus through monkeys and using the spinal cord from these monkeys for immunization of dogs. He began his treatment with a cord from a monkey injected with a virus that had been through a number of passages in monkeys, and for each succeeding injection used a virus of shorter passage, until he reached a virus that had been only once through a monkey.

From his success with this method of immunization, Pasteur simplified the method by using rabbits instead of monkeys; and he attenuated the virus by drying it for different lengths of time. He began treatment with a cord that had been dried for a number of days, and used a cord that had been dried a shorter time, until the final doses were with a cord that had been dried only three days.

As Pasteur's method of antirabic vaccination came to be used in numerous laboratories, various modifications of the method were developed.

Högyes held that Pasteur's method did not attenuate the virus, but that it diluted the virus, in that the virus died out gradually during the drying. On this basis, Högyes used undried cord, beginning with a dilution in such a dose that it would not cause rabies when injected into an animal, and gradually increased the dose.

Other laboratories attenuated the virus by heat, by the action of artificial gastric juice, by the action of glycerine, and by the action of one per cent. phenol solution.

The method was further modified by injecting serum of an immunized animal at the time the virus was injected, or by mixing the immune serum with the virus and injecting the mixture.

Ferran's method is of interest, in that it demonstrated that man stands large doses of undiluted and unattenuated fixed virus, without developing rabies. Ferran gave large doses of undiluted and unattenuated fixed virus subcutaneously; and a number of workers have injected large doses of fresh fixed virus into themselves without any untoward results. But Boreggio's unfortunate results followed injection of large doses according to Ferran's method.

Other methods are of scientific interest but not of practical importance.

Various workers showed that the injection of normal nervous tissue produced immunity against rabies; but Marx held that this was not a specific immunity, but only a non-specific increased resistance.

Where dried or attenuated virus is used, it is usual to inject constant or varying lengths of cord, beginning with the longer dried, or more attenuated, and gradually increasing to the shorter dried, or more virulent, cord. The table at top of page 538 may be taken as the type of this form of treatment.

In the case of severe bites, this course may be repeated in a month. This treatment is intensified in some institutes by giving two injections a day for five or six days in the beginning.

The Public Health Service method begins with six-day dried cord, and reaches a three-day dried cord on the fourth day of treatment. Children receive a smaller dose of the shorter dried cord than do adults.

Where the Högyes dilution method is used, it is usual to inject vary-

Day of treatment	Amount of cord	Age of cord	Day of treatment	Amount of cord	Age of cord
1st	2 c.c.	3 days	12th	2 c.c.	1 day
2d	2 c.c.	2 days	13th	2 c.c.	3 days
3d	2 c.c.	1 day	14th	2 c.c.	2 days
4th	2 c.c.	1 day	15th	2 c.c.	1 day
5th	2 c.c.	3 days	16th	2 c.c.	1 day
6th	2 c.c.	2 days	17th	2 c.c.	3 days
7th	2 c.c.	1 day	18th	2 c.c.	2 days
8th	2 c.c.	1 day	19th	2 c.c.	1 day
9th	2 c.c.	3 days	20th	2 c.c.	1 day
10th	2 c.c.	2 days	21st	2 c.c.	1 day
11th	2 c.c.	1 day			

ing amounts of different dilutions of the ground-up cord, beginning with a high dilution and gradually increasing to the stronger suspensions. The following table will serve as a type of this form of treatment:

Day of treatment	Dilution	Amount in cubic centimeters	Day of treatment	Dilution	Amount in cubic centimeters
1st A.M.	1: 10,000 + 1: 8,000	3—3	8th A.M.	1: 1,000	1½
P.M.	1: 6,000 + 1: 5,000	3—3	P.M.	1: 500	1
2d A.M.	1: 5,000	3	9th A.M.	1: 200	1
P.M.	1: 2,000	2	10th A.M.	1: 6,000 + 1: 5,000	3—3
3d A.M.	1: 2,000	2	P.M.	1: 2,000	2
P.M.	1: 1,000	1½	11th A.M.	1: 2,000	2
4th A.M.	1: 1,000	1½	P.M.	1: 1,000	1
P.M.	1: 500	1	12th A.M.	1: 1,000	1
5th A.M.	1: 200	1	P.M.	1: 500	1
6th A.M.	1: 6,000 + 1: 5,000	3—3	13th A.M.	1: 200	1
P.M.	1: 2,000	2	14th A.M.	1: 100	1
7th A.M.	1: 2,000	2			
P.M.	1: 1,000	1½			

For severe injuries, or injuries about the head, this course is often intensified by giving more and stronger emulsions, and by continuing the injections for twenty days.

The older methods of carrying out the antirabic vaccination require that one or more rabbits shall be inoculated every day, in order that there shall always be a supply of virus of the right age available. This is an extensive matter for small laboratories that have only occasional cases to treat. For this reason, there has been effort to develop a method by which it is possible to preserve the virus for some time. Chamberlain dried the cord the required number of days and preserved it in glycerine and found the virulence was normal for twenty days after drying. In this way, cord of proper length at time of drying can be kept on hand. Chamberlain did not understand that his was longer than two weeks in glycerine. This modification of the original Pasteur method has been in use at the Pasteur Institute in Paris since 1912—they do not use cord that has been longer than twenty days in glycerine.

Harris applied Shattuck's method of freezing and drying bacteria to the freezing and drying of the rabies virus in tissue. He found that the virus so dried and kept dry and cold retained its virulence unchanged for six months. This method of preserving the virus is used in connection with the dilution method of carrying out the antirabic vaccination.

For a number of years, evidence has been accumulating that a killed virus gives satisfactory immunity, and accordingly there is a growing trend of favor toward such virus. It has always been somewhat difficult

to know whether some of the viruses used were attenuated or were actually killed, as a killed virus will kill a rabbit, and it would be necessary to make further passages to determine whether the virus was only attenuated or was actually killed. Fermi's carbolized virus is probably a killed virus, at least in great part.

Semple took up the work of killed virus in India, and developed a method for killing the virus with phenol. That killed virus has been the official virus for immunization in India for some years, and the results have been entirely satisfactory. This virus keeps for several months, and can be sent out from the central laboratory and kept on hand at branch depots, so as to be available when needed. It also has the advantage that all doses are alike, it is necessary to give only fourteen doses, and it is not necessary for the patient to go to an institute for treatment.

Cumming kills the virus by dialyzing it against distilled water, with or without the addition of formaldehyde, and preserves it in phenol. The results from the use of this virus are excellent, and it is convenient and safe to use.

In some laboratories serum from rabies-immune animals—usually dogs—is used, in addition to the injection of the vaccine. Babes gives a course of vaccine in the regular way, and then gives two doses of 20 ml. each of immune serum, with one day intervening between the doses. Marie uses a mixture of the vaccine and immune serum, in which there is a slight excess of vaccine. The results from this method are entirely satisfactory.

In all methods, the injections are given in the right and left hypochondrium alternately.

With all of the methods, where the bites are numerous or especially severe, or are on the face, it is usual to intensify the treatment by giving more injections, and of more virulent virus, in the first few days.

Morison, using the Semple vaccine, in severely bitten cases, begins the course of treatment with five to seven doses of the vaccine intravenously.

Alivisatos, recognizing that severe bites and bites on the face require intensive treatment, mixes rabies cord with ether for 72 to 84 hours, then evaporates the ether, and injects the cord in large doses. His results have been excellent, and he gets no paralyses. Hempt uses the ether treated vaccine, giving large doses: cases with ordinary bites are given two doses daily for three to four days; cases with severe bites are given two doses daily for five days—never over two doses daily for six days for the most severely bitten cases. Hempt has treated 6000 cases, and none have developed rabies after 15 days.

Koch considers that potassium iodide is of value in the prevention of rabies; and every person is given a course of potassium iodide while taking the antirabic vaccination at Koch's Institute in Berlin.

Accidents during Antirabic Vaccination.—In general, there is no inconvenience from the vaccination. The local reaction is not severe, and the patient can be up and around during the vaccination.

Geiger has studied the *local reactions* of the Pasteur treatment. He finds that the local reaction very regularly appears on the seventh and eighth days, and on the fifteenth and sixteenth days. Occasionally a patient will have a reaction every day; and rarely will the patient have

no reaction at all. The reaction consists of an edematous area, with erythema, itching, pain and tenderness. The largest area of local reaction was 10 by 12 cm. Sometimes there is slight *general reaction* in the form of malaise and slight fever. He considers the reaction as due to hypersensitiveness to the nervous tissue injected; but he also notes that the reaction is more marked with the use of high potency virus.

Aside from the persons dying from rabies due to the animal bite for which they were being treated, there have been a few cases in which there seems to have been disturbance from the vaccination itself. In over 200,000 persons treated, Simon collected 103 that developed untoward symptoms during treatment, including those who developed rabies from the bite for which they were under treatment. Simon tabulated 100 cases of *paralysis* among 217,774 persons treated. Thus, of the persons treated, 0.048 per cent. developed paralysis.

Fielder collected 142 cases of "treatment paralysis." Mejia tabulates the cases of paralysis among persons treated at the Pasteur Institute in Buenos Aires: of 19,800 persons treated, 24 developed paralysis.

Cases of paralysis are very rare among persons treated by the Högyes dilution method: 3 cases in 51,417 persons treated, a per cent. of 0.0058. Paralysis is rare or does not occur in cases treated with virus killed by phenol, dialysis or ether.

Paralysis is usually more frequent after intensive treatment.

The paralysis usually develops about the fifteenth to the twentieth day—not infrequently as early as the eleventh day—after the beginning of antirabic treatment. Mejia used two methods of injections: one in which he gave 26 injections in nineteen days, and one in which he gave 19 injections in eleven days. When the shorter course of treatment was used, the paralysis came on the last day of treatment or the day after; that is, eleven or twelve days after the treatment was started. When the longer course was used, the paralysis came from one day to a week after the last injection; that is, sixteen to twenty days after the treatment was started.

One of Mejia's cases of paralysis was a child, six years old, which received 26 injections in fifteen days. The child was seen one month after completion of treatment, and was entirely well. A few days later, the child received a blow while playing in the hammock, in the morning. That afternoon, the child vomited; and paralysis developed the next day. Apparently the injury was not of such a nature that it could have been the direct cause of the paralysis.

In all of the cases of paralysis, the picture is very much the same. It begins with loss of appetite, mild fever, considerable stiffness in the back, and weakness in the legs. This weakness in the legs increases to complete paralysis, and ascends, involving the sphincters of the bladder and rectum. The paralysis may extend upward and involve the upper extremities and the face, and there may be bulbar symptoms. There may be disturbance of respiration and heart action and difficulty in swallowing. Mejia's cases of paralysis were in the form of transverse myelitis, multiple neuritis and ascending paralysis. The picture is frequently that of Landry's paralysis. There may be pain in the scar of the bite for which the person is being treated.

The condition lasts for two or three weeks, and recovery is complete. Remlinger collected 40 cases, of which 38 recovered. Of Simon's

tabulated 100 cases, 81 recovered; in Fielder's tabulated 142 cases, 118 recovered; and in Mejia's 24 cases, 20 recovered. As these tabulations, especially Simon's, include cases who developed rabies during the treatment, it appears that the mortality among persons who develop paralysis is not over 15 or 16 per cent. In Simon's tabulation, of the persons treated, 0.00912 per cent. died of rabies or of paralysis.

It is not easy to explain these paralyzes, and it has been suggested that they are due to various causes, as follows:

1. Abortive cases of the paralytic form of rabies, resulting from the bite for which the person is being treated, which recover under the antirabic treatment.
2. Abortive cases of the paralytic form of rabies, due to the fixed virus inoculated.
3. The toxin of the rabies organism.
4. The toxic action of the material used in the injection, other than the toxin of the rabies organism.
5. Hypersensitiveness.

It is possible that the condition may be due to more than one of the above causes. Fielder considers it as generally due to the fixed virus used in the treatment; either a virus infection or the toxin, or both. Fixed virus has been found in the brain of some cases dead of treatment paralysis; in other cases, no rabies virus was found in the brain.

Mejia considers the paralyzes are due to the virus itself, and warns against too rapid pushing of the treatment. He says that certain people have an idiosyncrasy, and that some organisms do not react as well as others in the presence of toxic or infectious substances.

The Vienna Rabies Institute had 35 cases of paralysis from 1915 to 1924, of which 8 died. All animals inoculated from the central nervous system of these cases were negative. Schweinburg carried out a series of inoculations on rabbits, using normal human spinal cord, prepared in different ways, for the inoculations. Each rabbit was given 14 daily injections. Cord dried at room temperature or by heat, as well as fresh undried cord, caused paralysis in about 20 per cent. and death in about 5 to 8 per cent. of the rabbits. Normal cord, injected in the same way by the Högyes dilution method, did not injure any of 56 rabbits in the series. Schweinburg is of the opinion that the injected nerve tissue is the cause of the paralysis.

The rarity of the condition following use of the dilution method and the killed virus methods of treatment is important. The possibility of bacterial contamination of the material used for injection should be kept in mind and guarded against. Isabolinsky says that the rabbit cord is bacteriologically sterile when removed, and that any bacterial contamination occurs in the subsequent handling of the material.

Personal idiosyncrasy plays an important part in the development of these treatment paralyzes. The condition rarely affects children. It is more common in syphilitics, alcoholics, persons under nervous strain, and brain workers, and is especially common in soldiers—as much as four times as common as in civilians. But, after all, it must be remembered that a laboratory may go for a number of years without a case of paralysis, and then, without changing its methods in any way, have a number of cases. It is to be remembered that persons who have been bitten by a dog are likely to have nervous and hysterical symptoms.

So, it is evident that antirabic vaccination is not without an element of danger, and should not be given unnecessarily.

Contra-Indications to Antirabic Treatment.—There are no contra-indications. The treatment is stopped if the patient develops rabies or treatment paralysis during the vaccination. Other diseases, or pregnancy, are not contra-indications. There may be relapse of malaria during the vaccination but it is to be treated in the usual way. The tendency to treatment paralysis in syphilitics is not a contra-indication to anti-rabic vaccination, but calls for treatment of the syphilis.

Availability of Antirabic Vaccination.—Commercial firms and Boards of Health throughout the country prepare the vaccine for antirabic vaccination and send it out in syringe containers, ready to inject; full instructions accompany each package of vaccine. In the United States, sixteen establishments are licensed to propagate and sell rabies virus; and at least six State Boards of Health and one City Board of Health prepare the vaccine for use within the state or city. The types of vaccine furnished by the commercial firms are as follows: Dried cord (Pasteur) 9; Diluted (Högyes) 2; Diluted (Harris) 2; Killed (phenol) 5; Killed (dialyzed) 1. In the state and city laboratories, the types are as follows: Dried cord (Pasteur) 4; Diluted (Högyes) 2; Killed (dialyzed) 1.

With the development of methods of preserving the vaccine and sending it out for use, it is not necessary for each state or city to maintain a laboratory for preparing the vaccine; and Sellers says it is not advisable for a state or city to maintain a laboratory where the demand does not exceed 200 treatments annually. In only eight states did the number of treatments exceed 200 in 1921.

Sellers tabulated the types of treatment, in 1921, in 31 states that answered his questionnaire.

Method	Number of States	No. of Treatments in 1921
Dried (Pasteur).....	24	5,301
Dilution (Högyes).....	2	1,257
Dilution (Harris).....	3	82
Killed (dialyzed).....	2	81

Georgia has since changed from dried cord to the Högyes dilution method.

The provision for furnished treatment varies in different states. In 1921, Sellers tabulated the provision for furnishing treatment.

Fifteen states make no provision for furnishing treatment.

Seven states provide free treatment to all.

Thirteen states provide free treatment to persons unable to pay, and at cost price to those able to pay.

One state provides free treatment to persons unable to pay, and at full commercial price to those able to pay.

Results of Antirabic Vaccination.—The probability of failure of anti-rabic vaccination depends on a number of factors. The nearer the bite is to the central nervous system the greater the danger, as with wounds on the face or head; wounds on uncovered parts of the body are more dangerous than when the bite is through the clothing; the number and extent of the bites is of importance; the most dangerous bites are, in descending order: those of wolves, jackals, cats, dogs and other animals. Of 569 persons treated at the Shillong Pasteur Institute in 1917, 5 died

of rabies—4 of these being bitten by jackals. One jackal was reported to have bitten as many as thirty people. It is to be remembered that a dog, in licking a wound, or soiling it with froth from the mouth, may inoculate with rabies; and there seems to be some indication that superficial wounds and abrasions are apt to be dangerous, possibly because they usually get no local treatment at all. Cumming points out the importance of prompt and energetic treatment of the wound, as any rabies virus left in the wound multiplies and will tend to overcome the immunity produced by the antirabic vaccination. Of less importance is the age of the person, antirabic vaccination being more likely to fail with young persons than with older persons.

Of great importance is the length of time after the bite before the beginning of the protective vaccination. Where the wounds are severe, and a period of ten days has elapsed since they were received, it is not possible to prevent rabies by antirabic vaccination. Where the patient comes late for treatment, it is possible to give an intensive course of treatment, and thus lessen the danger of failure; but in many such cases the virus has already spread in the nervous system and the vaccination fails. The virus inoculated by the bite multiplies, and if vaccination is delayed, the dose of virus may have increased to where it overcomes the immunity developed as a result of the vaccination. In addition to this, there are cases in which the treatment is begun early and is carried out properly yet the patient develops rabies. It seems that in such cases there has been a failure on the part of the tissues to elaborate antibodies, just as there may be failure to develop antibodies against any infection. In other cases the vaccination merely holds the virus in check, and a shock or injury, perhaps months afterwards, may lead to development of rabies.

Using the frozen and dried virus by the dilution method, Harris says the time required for immunization is shortened over the dried cord method by more than half. He collected reports of 1159 persons who had been treated with the frozen and dried virus by the dilution method. No person developed rabies after fifteen days following the last injection. One patient died during treatment and one died fourteen days after the first injection. There were no paralyses. The proportion of persons developing paralysis from the dilution (Högyes) method, is about one in 17,000.

It is considered that at least fourteen days must elapse after completion of the vaccination before the person is immune, and on that basis it is usual to eliminate cases developing rabies during the treatment, or within fifteen days after completion of the treatment, in calculating the value of antirabic vaccination.

Not all persons bitten by a rabid animal will develop rabies, the proportion being given as about one in six. Since it is impossible to determine whether a large part of the persons receiving antirabic vaccination were bitten by rabid dogs, it is not possible to say what proportion of the treated persons fail to be protected.

In determining the results of vaccination, the patients are divided into three classes, according to the information available as to whether or not the biting animal was rabid:

Class A. Cases where the biting animal is proven to be rabid by natural or experimental inoculation.

Class B. Cases in which the biting animal is diagnosed as rabid by a veterinarian. (Certified rabid.)

Class C. Cases in which the biting animal is suspected of being rabid.

The following table of persons treated at the Pasteur Institute, Paris in 1924, gives an idea of the results of vaccination in these different classes:

Year 1924	Bite on Head			Bite on Hands			Bite on Limbs			Total		
	Treated	Died	Mortality per 100	Treated	Died	Mortality per 100	Treated	Died	Mortality per 100	Treated	Died	Mortality per 100
Class A.....	10	0	0	94	0	0	31	0	0	135	0	0
Class B.....	15	0	0	118	0	0	75	0	0	208	0	0
Class C.....	23	0	0	206	1	1.20 (sic)	192	0	0	421	1	0.23
Total.....	48	0	0	418	1		298	0		764	1	0.14

From its establishment in 1886 to the end of 1924, the Pasteur Institute in Paris vaccinated 46,062 persons, of whom 151 developed rabies after an interval of 15 days following the completion of the treatment; that is, 0.33 per cent.

Remlinger collected the statistics of all institutes over varying periods of years; and his table shows that of 152,859 persons vaccinated, 705 (0.46 per cent.) developed rabies after an interval of 15 days following the completion of vaccination. There are great differences in the results from different institutes, the higher percentages of failures probably being where wolf bite is more frequent, where it is difficult for the people to obtain treatment, and where the people are careless about prompt treatment.

Immunity Following Vaccination.—The immunity in man, following vaccination, lasts about a year. Williams cites the case of a man who developed rabies 14 months after antirabic vaccination, and 6 weeks after exposure to infection.

Marie found dogs immune 18 months after vaccination. Ravenel states that in dogs the protection has disappeared, at the end of one year in 21 per cent., and at the end of two years in 33 per cent.; while it persists for five years in others.

Mechanism of Immunity.—Fixed virus, injected into man, is killed before it reaches the central nervous system; and the organisms, being broken up, act as antigen and lead to development of rabicidal substances which circulate in the serum of the vaccinated person. This development of rabicidal substances can be demonstrated in vaccinated animals. There is undoubtedly a tissue immunity, as is found in other immunity reactions, as vaccinated animals are immune after it is no longer possible to demonstrate rabicidal substances in their blood.

Dilutions of virulent material lead to active development of rabicidal substances; while dried, avirulent material leads to the production of a much lower grade of immunity. From this, it appears that the immunity results from the breaking down of the rabies organism itself and not from the rabies toxin. Since it is possible to produce increased resistance to rabies infection with injections of normal nervous tissue, it is necessary to remember that the immunity produced by the dried, avirulent material may be of the nature of a non-specific increased resistance,

rather than specific immunity. But the results with the killed virus are so good in practice that we must suppose the immunity developed by the dead virus, while probably not as high as that produced by the living virus, is high enough to protect against the usual dose of virus inoculated by the ordinary bite.

Heredity of Immunity.—Exceptionally, in animals, an immune mother transmits immunity to the young through the placenta; but this immunity is never transmitted to the next generation.

TREATMENT OF THE DEVELOPED ATTACK OF RABIES.—The patient should be put to bed and kept there, a restraint apparatus being used if necessary. As any stimulus brings on the spasmodic attacks, the room should not be brightly lighted, and there should be no sudden noises, drafts of air or other sudden stimuli. Generally, liquids cannot be swallowed; but semi-solids can often be swallowed. **Ice cream** and **custards** may be taken. When nothing can be swallowed, food may be given by rectum, and thirst may be relieved in the same way.

The ordinary sedatives have very little action in controlling the spasms; but it is advisable to give **morphine** hypodermically, in an effort to diminish the severity of the spasmodic attacks. Inhalation of chloroform may give relief from the attacks; and **chloral** and **bromides** may be given by enema. **Curare** and **calabar bean** have been recommended, and there are reports of recovery under the use of **curare**. **Atropine** is advised by some of the authorities in India.

Moon and Harris reported cures of rabies from the administration of **quinine**; Haberlin reported a cure from the injection of **phenol solution** after the manner of Bacelli's method for the treatment of tetanus; and Tonin reported a cure from the use of **salvarsan**. Unfortunately, further trial has not confirmed the value of any of these methods of treatment.

Prognosis.—It is generally held that rabies in man is fatal in 100 per cent. of the cases, and that the reported cases of recovery are cases of lyssophobia. It is pretty definitely agreed that there are occasional cases of recovery in dogs. D'Aunoy reports a case of spontaneous recovery in a rabbit experimentally inoculated with fixed virus. While it is possible to transmit rabies to birds, chickens and pigeons, the disease is usually mild, and tends to spontaneous recovery.

The development of rabies in man can be prevented by prompt prophylactic inoculation in over 95 per cent. of the cases bitten.

Mechanism of the Disease Process.—When rabies virus is naturally or experimentally introduced into the body of the animal, it travels to the central nervous system along the nerves or through the blood and lymph. It is generally held that along the nerves—possibly in the lymph spaces in the nerves—is the usual route of the virus; through the blood and lymph channels being unusual. Section of the spinal cord prevents the passage of the virus from the leg to the brain, and the part of the central nervous system nearest the bite is the part that shows the first evidence of the virus. In the same way is explained the longer incubation period when a person is bitten on the leg or arm as compared with a bite on the face—that is, closer to the brain. On this basis, the virus reaches the salivary gland by traveling down the nerve from the brain. The authorities who hold the view that the virus travels along the nerves

are of the opinion that the long incubation period is, in great part at least, represented by the time it takes the virus to travel along the nerves to the central nervous system.

Koch is of the opinion that the virus spreads through the blood and lymph channels very generally; and that this is probably the more common way of spread of the virus in the body. On this basis, the virus is picked out from the blood especially by the nervous tissue, whether it be in the central nervous system or in the salivary glands. The virus is present in the blood of a rather small percentage of animals at the time of death from rabies; but it is undetermined whether the frequent presence of the virus in the suprarenals, and the less frequent presence in the spleen and pancreas, is from a primary infection of the blood or from a secondary infection of the blood from the central nervous system.

According to Fermi, the rabies virus passes through the unbroken mucous membranes of the nose, conjunctiva and intestine, in fifteen minutes; but Rochaix and Papacostas say that the intestinal mucosa is not permeable for the virus. When inoculated into the anterior chamber of the eye, it takes the virus twenty-four hours to reach the outside of the eyeball. Immediate cauterization of the wound does not surely prevent rabies; but half of the experimental animals are saved when the bite is cauterized within thirty minutes. This rapid passage of the virus is considered by some authorities to favor the opinion that it travels by the blood and lymph channels. The authorities who hold the view that the virus commonly travels in the blood or lymph channels are of the opinion that the long incubation period is due to the virus remaining for some time in the central nervous system before it has multiplied enough to produce lesions.

The lesions of rabies are due to the toxin produced by the virus. Babes is of the opinion that the disturbances of the nervous system, including paralysis, following prophylactic inoculation with rabies virus, are due to the toxin of the rabies virus. Babes also considers that the leucocytosis, which is present even before symptoms appear, accounts for the plugging of the capillaries and the small areas of softening in the brain. But there is difference of opinion as to the cause of the paralyzes, and Schweinburg has produced paralysis by the repeated injection of normal human brain.

Immunity.—Since animals rarely recover from rabies, little is known regarding immunity following an attack of the disease. D'Aunoy studied the serum of his rabbit which recovered from rabies; the serum of this rabbit, seventeen and ninety days after inoculation, had no appreciable antirabic effect. On the fortieth day after inoculation, this rabbit received twice the original infecting dose of rabies virus subdurally, and remained well. The mechanism of immunity following antirabic vaccination is discussed under vaccination in this article.

Cause of Death.—In the stage of excitement, death is due to apoplexy, or to asphyxia during a convulsion. In the paralytic stage, death is due to the degeneration of the tissues of the central nervous system and to the intoxication.

Pathology.—*MACROSCOPIC.*—In general, there are no characteristic gross changes in the animal dead of rabies. There is emaciation; and there is a catarrhal condition of the mucous membrane of the nose and mouth. There may be no changes in the central nervous system. More

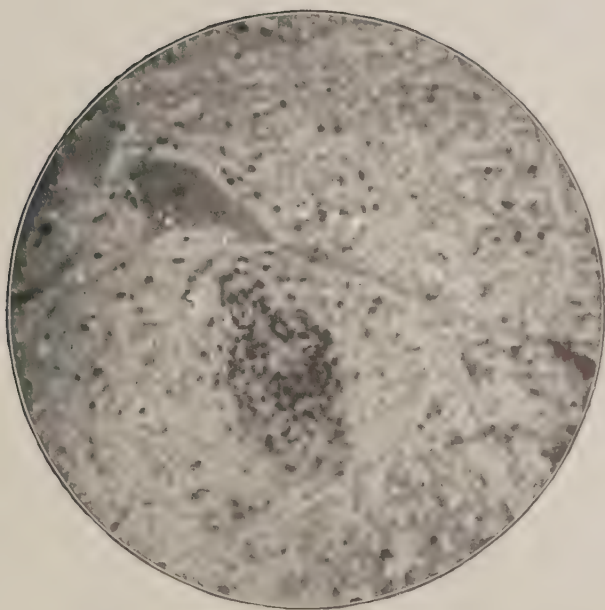


FIG. 1.—RABIES TUBERCLE IN THE MEDULLA. (From Ravenel, in Osler and McCrac's
"Modern Medicine," Lea & Febiger.)



EXPLANATION OF PLATE I.

Section through the hippocampus of a rabbit which died twenty days after intramuscular inoculation of brain emulsion from a rabid dog. Lentz staining method B. Zeiss compens. oc. 12, obj. apochromat. 2 mm. homog. immersion, N.A. 1.30, tube length 160 mm.

The nerve cell to the right at the top shows marked degeneration. The nucleus stains a dull violet, and is not marked off from the cell cytoplasm, while the nucleolus stains a deeper blue than in the other nerve cells. The Negri body in the upper part of the cell stains faintly, and has four rather large "inner bodies"; while one "inner body" in the lower Negri body is unusually large. These bodies are probably closely related to the Lentz "passage bodies." The Negri body in the cell at the left side of the plate lies on top of the nucleus.

(From Dudley and Whitmore, in *Philippine Journal of Science*.)

commonly, the brain and meninges are congested and edematous, and there may be pin-point hemorrhages and areas of softening in the depth of the brain and cord; the areas of softening in the cord being especially common in man. The softening in the spinal cord is especially common when the animal has died of paralytic rabies.

The stomach is shrunken, and contains no food; but is filled with foreign substances, as sticks, stones, hair, straw, leather, and any other foreign substance the dog may have picked up during the period of excitement. There are often hemorrhagic erosions in the gastric mucosa, but this is probably not connected specifically with rabies.

MICROSCOPIC.—In a section of the central nervous system, as the spinal cord, one of the striking things is the blood vessel changes. The blood vessels are dilated and packed with red cells, and in places there are minute aneurysms or ruptures of the vessel wall, giving rise to the minute hemorrhages that are seen in the gross specimen. These hemorrhages may destroy the surrounding tissue, and produce the areas of softening. The vessel walls are thickened and are infiltrated with leucocytes; the perivascular lymph spaces being filled with leucocytes. There are hyaline areas in the vessel walls, and some vessels are plugged with masses of leucocytes or fibrin. These changes are especially marked in the anterior and posterior horns and about the central canal, in the spinal cord.

But it is in the nerve cells in the central nervous system that the most striking changes are found in rabies. The outline of the ganglion cells becomes indistinct; the nucleus is granular and stains diffusely with eosin, and shows hyaline change. The cell is vacuolated or may contain large spaces; and when the process has lasted some time the cells may be changed to granular, fatty masses. In cases of long duration, there is granular and fatty change in the neuroglia cells. About these degenerated ganglion cells is the same leucocytic infiltration that is found about the blood vessel walls; and these areas of infiltration about the blood vessel walls and the degenerated nerve cells, scattered through the central nervous system, are the "rabies tubercles" of Babes (Fig. 1).

The specific finding is the Negri bodies in the ganglion cells in the central nervous system (Plate 1). Manouelian reports the finding of Negri bodies in the cytoplasm of the ganglion cells in the salivary glands. The gland epithelium degenerates and is taken up by endothelial cells. No Negri bodies are found in the gland epithelial cells.

Lentz described peculiar bodies in the large pyramidal cells in the hippocampus major of rabbits that had been inoculated with passage virus. From their resemblance to Negri bodies, and their presence in the brain of animals inoculated with passage virus, Lentz called them "passage bodies," and considered them specific for passage virus. Other authorities have considered these bodies as degenerated cells, such as are found in rabbits which have been poisoned with diphtheria toxin, and hold that they are not specific.

The change in the central nervous system is inflammatory in nature, and was considered an acute myelitis by Schaffer. Golgi considered it as a parenchymatous encephalomyelitis which combined irritative and degenerative changes. The changes in the nerve cells and neuralgia are due to the action of the toxin formed by the virus, which has a special affinity for the central nervous system.

In the fatal cases of treatment paralysis, the pathological picture is, in the acute cases, that of a transverse myelitis, varying from marked congestion, through a hemorrhagic myelitis, to where the cord tissue is reduced to a soft structureless pulp; and, in the more chronic cases, a more diffuse degeneration, with cellular infiltration.

History.—It is convenient to divide the history of rabies into four periods, the first period going back to ancient times. Akteon, son of Aristeus, died of rabies about thirteen centuries B.C. (Yount). The disease was well known in Aristotle's time (384 to 322 B.C.) as he writes: "Dogs suffer from madness. It throws them into a state of fury, and all animals which are then bitten are also attacked with madness, with the exception of man." It is quite possible that this refers to the form of the disease, rather than that man was not considered to have rabies. Human rabies was well known at the time of Celsus, in the first century A.D. From this time until 1800, little was added to the knowledge of rabies. Indeed, it was during the latter part of this period that were developed so many of the ideas that still are not entirely dead: Zwinger's idea that a non-rabid dog could transmit rabies to man; and Bosquillon's idea that there was no special rabies virus, but that fear alone could produce the disease. Meads, in 1767, and van Swieten, in 1770, described the paralytic form of human rabies.

The second period began in 1804, when Zinke transferred rabies from an infected animal to another animal, by painting the saliva of a rabid dog onto a fresh wound on another dog, the second dog developing rabies. He also transmitted the infection to a rabbit and to a chicken in the same way. The method of transmitting rabies from dogs to rabbits was developed, and, in 1879, Galtier showed that this was a good method of determining whether a dog had rabies; and Raynaud showed that the rabies virus could be transmitted from man to rabbits. In 1826, von Krügelstein expressed the opinion that the rabies virus was in the central nervous system; and Duboué, in 1881, confirmed this finding, and considered that the virus reached the central nervous system by way of the nerves.

The work of Pasteur and his co-workers marks the third period in the study of rabies. Pasteur began his work in 1880, and announced his results at the International Medical Congress in Copenhagen, in 1884. Pasteur showed that the rabies virus is constantly in the central nervous system of rabid animals; and that subdural injection of small amounts of the brain or spinal cord of rabid animals into susceptible animals constantly produced rabies. He showed that, when the rabies virus from dogs is injected into rabbits, after a few passages the virulence of the virus for the rabbit is increased until it kills in a short time. This virus no longer produced rabies in dogs, but rendered them immune to a subsequent injection of virus from a dog. He applied this method to the immunization of persons bitten by rabid animals—with the results we know today.

The fourth period in the history of rabies began in 1903 with Negri's discovery of the small bodies in the ganglion cells in the central nervous system of rabid animals. The regularity with which these bodies are found in the brain of rabid animals makes it possible to make the diagnosis in 90 per cent. of the animals that die of rabies, without having to wait for the disease to develop in inoculated animals.

Geographical Distribution and Prevalence.—Rabies occurs in all parts of the world, in cold as well as warm climates. It has not been observed in South and Central Africa; and it has not been reported from Siberia, though it is common in Russia. Australia is free from the disease as a result of exclusion of the disease by rigid quarantine. As a result of rigid quarantine and muzzling of dogs, England was free from the disease for twenty years; it reappeared during the World War. as a result of avoidance of the regulations; and has been wiped out again as a result of rigid enforcement of the regulations. Oulow Fato, in West Africa and Sudan has been identified as rabies. The disease increased in Europe after the World War, but is decreasing again. The disease is fairly common in the United States; there were 690 deaths from rabies in the registration area in 1913 to 1924 inclusive. In 1923, 22,000 persons applied for antirabic vaccination in the United States.

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CHAPTER XIX

MALARIA

By CHARLES C. BASS, M.D.

Etiology, p. 551—Predisposing causes, p. 551—Exciting cause: the malaria parasite, p. 564—Morphology and development, p. 564—Distribution of malaria parasites in the body, p. 573—Cultivation of malaria plasmodia, p. 573—Distribution of malaria parasites outside of the body, p. 579—Modes of conveyance, p. 579—Types of infection, p. 584—Symptomatology, p. 584—Clinical history, p. 584—Physical findings, p. 594—Laboratory findings, p. 597—Special examinations, p. 602—Diagnosis, p. 602—Complications and association with other diseases, p. 606—Sequelæ, p. 607—Clinical varieties, p. 610—Treatment, p. 612—Prophylaxis, p. 612—General management, p. 626—Diet, p. 627—Climatology, p. 627—Local treatment, p. 628—Treatment of symptoms, p. 628—Specific therapy, p. 628—Medicinal treatment, p. 628—Surgical indications, p. 632—Management of convalescence, p. 633—Prognosis, p. 633—Pathology, p. 637—Historical summary and distribution, p. 641—Sociological aspect, p. 642.

Etiology.—1. **PREDISPOSING CAUSES.**—(1) *Cold, Extremes of Temperature.*—Exposure to extremes of temperature cannot cause infection with malaria, except that possibly such influences may increase the susceptibility to infection of people who otherwise possess a considerable degree of immunity, if such a thing exists. People already infected (malaria carriers, who are sources of infection without themselves having attacks) frequently have attacks of chills and fever or other clinical forms of the disease following sudden chilling of the surface of the body, especially if they are very warm at the time. It has been frequently noted that laborers or other individuals in intensely malarious sections who are infected but present no symptoms at the time frequently begin to suffer from chills and fever as soon as the rainy season sets in, and often considerably in advance of the time necessary for a new crop of *Anopheles* to grow, become infected and transmit malaria. The author was told by Dr. Carter and Dr. James that in the Canal Zone, whenever the rainy season sets in, there is a great increase in the cases of malaria admitted to the hospitals, even in the first week or two. They attributed this to the fact that the laborers are drenched by showers while out at work. The sudden chilling of the body brings on the symptoms. The increase occurs in a much shorter time than is required for an increased crop of mosquitoes to result from the rainy season and for them to become infectious.

(2) *Climate.*—A dry climate is opposed to malaria and a wet cli-

mate favors it. This fact is due to the influence upon the production of *Anopheles*. The longer the rainy season in any locality, the more favorable that locality is for *Anopheles* and, of course, for the transmission of malaria. Generally speaking, the nearer we approach the tropical climate, the greater the intensity of malaria. Though *Anopheles* can withstand a great deal of exposure to cold, even the larvæ passing through quite severe winters, they are not active during cold seasons and therefore a cold climate is opposed to the transmission of malaria. Generally speaking, the longer the cold season, the less malaria, and the longer the warm season, the more malaria.

(3) *Season*.—The season of the year which is the most favorable for the transmission of malaria is the one also most favorable for the development of *Anopheles*, namely, the warm season. In the southern

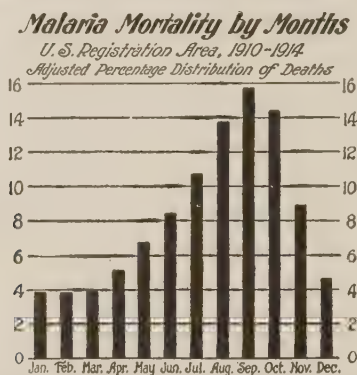


FIG. 1.—CHART SHOWING MALARIA MORTALITY BY MONTHS (Hoffman, Courtesy Prudential Press).

United States the malaria transmission period is from about May 1st to November 1st. The most favorable period of transmission is the entire warm season. It is a fact that there is a greater tendency for infected persons to develop clinical symptoms during the spring and fall than during the summer months, probably due to the greater daily variations in temperature during these seasons. Tertian malaria is much more frequent during the spring and early part of the summer than estivo-autumnal, which is more frequent during the late summer and fall. Clinical attacks of malaria rapidly decrease upon the appearance of cold weather. Usually in the southern states, during the months of December, January and February, there is a great reduction. It is to be supposed that little or no transmission is taking place during this period and that the cases that do develop are relapses. Though there is a great reduction in the cases of the disease at this time, some cases occur even during the coldest season. Malaria mortality by months in the United States registration area is shown in Fig. 1 from Hoffman.¹

During the past several years the United States Public Health Service

has gathered information from the physicians of several different southern states as to the prevalence of malaria from month to month. These have been included in the Public Health Reports and also published as reprints.²

A representative chart (Fig. 2) is reproduced here. It is noteworthy that the high point is reached in September in every state.

(4) *Altitude*.—The higher the altitude, the less likely is transmission of malaria to take place. In tropical countries, where the low-lying valleys are notoriously malarious, the high, mountainous country is usually more or less free from the disease. Not only is a high alti-

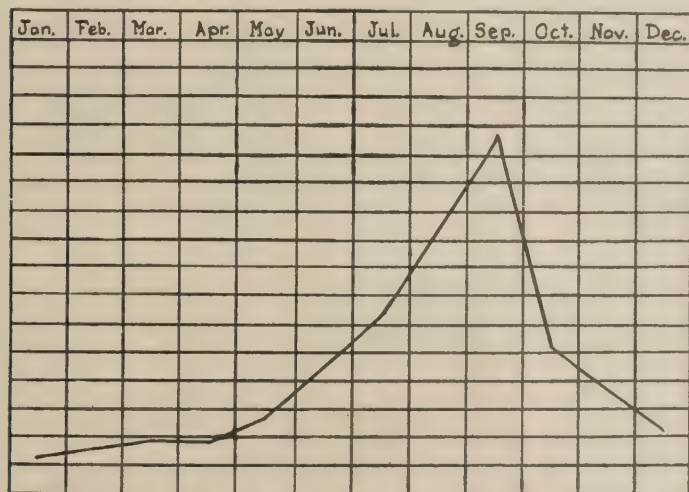


FIG. 2.—RELATIVE PREVALENCE OF MALARIA IN ARKANSAS, BY MONTHS, AS INDICATED BY THE NUMBER OF CASES REPORTED. (U. S. Public Health Report No. 451.)

tude unfavorable for the transmission of malaria, but it also seems to favor recovery from the disease in individuals who are already infected. Perhaps this is the result of the general invigorating effect of the high altitude. Frequently individuals who are infected and have perhaps not shown any symptoms at all in a low, malarious country, promptly have attacks whenever they go to high altitudes. These attacks are, however, usually followed by more rapid recovery and more certain disinfection than takes place in the lower altitudes.

(5) *Soil*.—The more impervious the soil is to water, the more favorable it is for the production of mosquitoes and therefore for the transmission of malaria. Porous, sandy soil is least favorable for the collection of water in pools, ponds, etc., and therefore least favorable for mosquito-breeding and the transmission of malaria.

(6) *Sex*.—Malaria is slightly more prevalent among males than

among females. Our Bolivar County investigations, including 31,459 persons, showed by blood examination 21.44 per cent. infection in males and 19.83 per cent. in females.

(7) *Age*.—Malaria has been generally thought to be more prevalent in children than in adults. A blood examination of 31,459 persons in our Bolivar County experiments showed this to be the case. The greatest prevalence is reached at the age of six. Fig. 3, taken from the report of this work made to the International Health Board, shows the percentage of infection found in the ages under twenty over a period of two years; and Fig. 4 shows graphically the percentage by age groups.

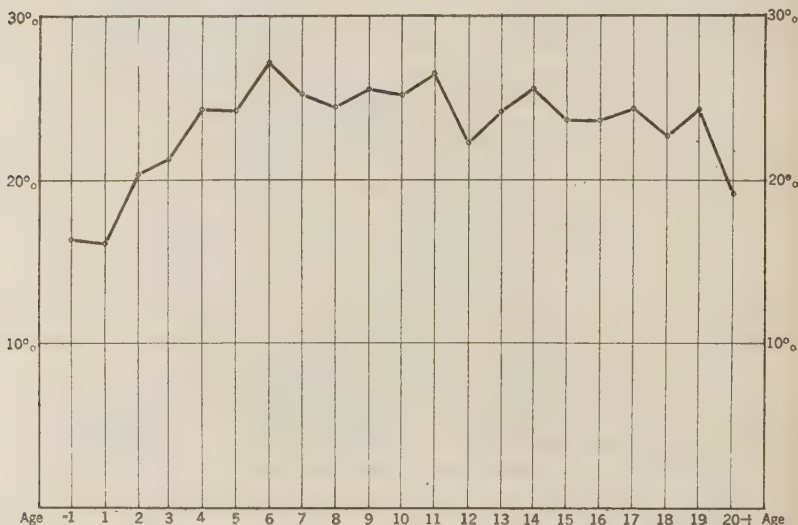


FIG. 3.—BLOOD INDEX BY YEARS, TO 20 YEARS; FIRST EXAMINATION 31,459 PERSONS.

The great importance of malaria to the youth of the country is shown more impressively by Fig. 5, in which the distribution by ages of the total amount of malaria found is shown.

(8) *Race*.—Deaderick³ says:

“Caucasians residing in non-malarial countries are, when exposed, most liable to contract malaria. Negroes bred in highly malarial regions are, as long as they remain upon their native soil, least susceptible to paludal infection.

“Immunity within the race increases generally as we go toward the equator. Thus the negroes of the Southern States display less immunity than the negroes of the West Indies or of tropical Africa. Likewise it may be said that immunity is much more marked in countries with a high than in those with a low endemic index.

“The immunity of the negro race has been variously estimated, some observers maintaining that they are absolutely proof against ma-

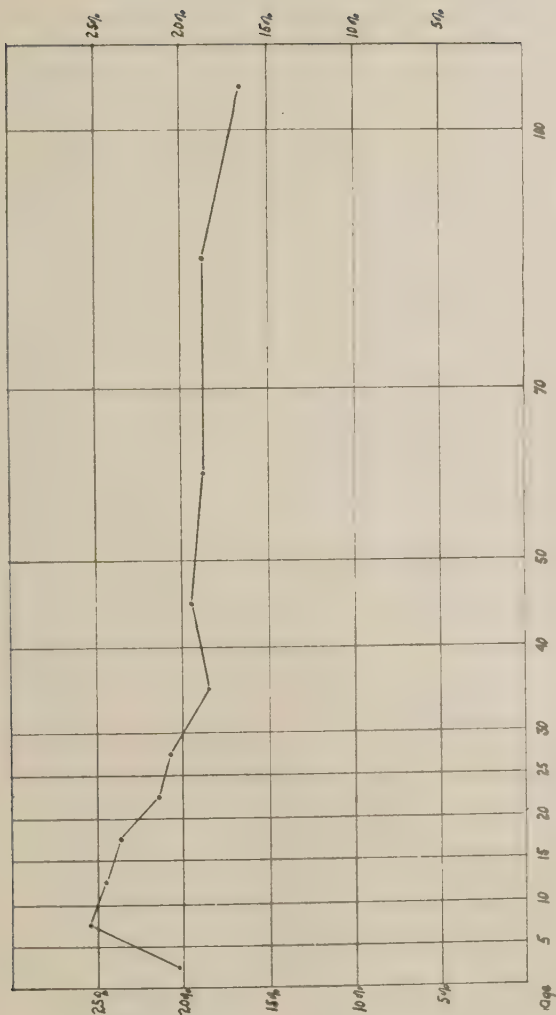


FIG. 4.—BLOOD INDEX BY AGE-GROUPS; FIRST EXAMINATION 31,459 PERSONS.

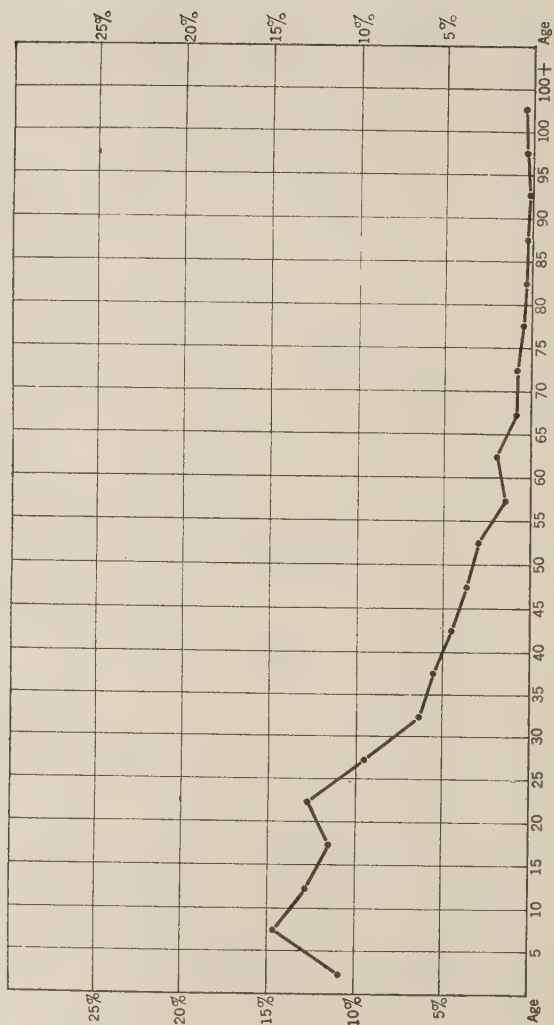


Fig. 5.—CHART SHOWING THE PERCENTAGE OF ALL THE MALARIA FOUND BY FIRST BLOOD EXAMINATION OF 31,459 PERSONS, IN EACH FIVE-YEAR AGE-GROUP.

larial invasion, while others hold that they are as susceptible as the whites. The truth lies between these two extremes. Adult negroes reared in malarial regions are much less liable to paludism, as long as they remain indigenous, than are the whites. The negro race does not, however, enjoy an absolute but only a relative immunity from malaria."

A blood examination of 31,459 persons in Bolivar County showed that 16.99 per cent. of whites were infected as against 22.21 per cent. negroes. There was therefore 30.72 per cent. more malaria found in negroes than in whites. It is believed that this is the largest number of systematic blood examinations of white and colored individuals living in the same locality and under practically the same conditions in close association with each other that has ever been made. It is probable that these figures are more trustworthy and more certain to indicate the facts than is any other source of information at present available. A blood examination was made of everybody living within an area of more than 300 square miles.

(9) *Heredity: Family Predisposition*.—Malaria parasites cannot pass from the mother to the fetus and there is therefore no inherited malaria. It is a fact that the maternal side of the placenta is frequently loaded with malaria parasites. A new-born child has no malaria parasites, but is of course susceptible to infection, and if it is born in a house where the mother and perhaps other members of the family suffer from malaria, the chances of early infection are great. It is not uncommon to see babies not more than two or three months old who have become infected with malaria under these circumstances. Sometimes there seems to be a very marked family predisposition to the disease. This, however, is only apparent. The cause of the apparent predisposition is the fact that the family are all exposed to infection.

In this connection, the author wishes to emphasize, if possible, the very great importance of family transmission of malaria. If one member of a household is infected, there is a much greater chance of transmission from him to other members of the same household than to persons living in other houses. This is especially true in rural districts where residences are usually some distance apart. *Anopheles* mosquitoes have a habit of taking their blood-meals at the same house, or, at least, they show a tendency to do so. Of course, if houses are located close together, there would be less chance of an infected mosquito's returning to the same house to get another blood-meal than would be the case if the sources of supply were farther apart. This fundamental fact, underlying the malaria problem and especially the problem of malaria control, can be taken into account to great advantage.

(10) *Personal Condition: Individual Susceptibility*.—Experimental inoculation of people who have not previously had attacks of malaria indicates that all or practically all persons are susceptible to infection, and certainly in almost all cases suitable infection results in clinical symptoms of malaria. We may therefore look upon all persons as being susceptible, although naturally a greater susceptibility may be found in one individual than in another. Isolated or repeated previous attacks,

especially during childhood, result in a degree of resistance sufficient to prevent clinical symptoms in a large per cent. of cases, although perhaps not sufficient to prevent infection. It seems also that the amount of infection introduced has something to do with whether or not an individual develops clinical symptoms. Therefore, although an individual might escape the disease if bitten by only one or two infected mosquitoes, he would be apt to develop it if bitten by hundreds of infected mosquitoes. As has been seen, certain influences, such, for instance, as sudden exposure, chilling of the body, overeating, indigestible food, etc., may precipitate attacks in susceptible individuals who otherwise might not have clinical attacks. It is reasonable to suppose that individuals who possess sufficient resistance or insusceptibility to prevent their becoming infected under ordinary circumstances might become infected if the inoculation took place at times when their normal resistance was greatly reduced.

Not only is there individual variation in susceptibility to infection, but there is also great variation in susceptibility to the clinical effect of the disease. It frequently occurs that in a family or group of people who have been exposed to infection, one or more may have ordinary chills and fever, others may be malaria carriers without showing any recognized symptoms, and another one or two, perhaps infected from the same source, may develop pernicious malaria and die. For this reason, an individual infected with malaria, whether he is simply a malaria carrier without clinical symptoms or a mild case, may be the source of the worst form of malaria and death to his family and to those with whom he lives in close contact and to whom he is therefore likely to be a source of infection.

(11) *Social Conditions: Class Diseases.*—(a) *Cities versus Country.*—Malaria is a rural and not an urban disease. Under conditions favorable for the production of *Anopheles* it sometimes happens that they are present in cities of considerable size and may transmit malaria. In the built-up sections of cities there are usually few favorable breeding places for *Anopheles*. Cities in the tropics that are surrounded by jungles and ideal breeding and protecting ground are usually badly infected. *Anopheles* fly, under varying conditions, and may transmit malaria as far as half a mile from their breeding ground and protecting forest or jungle; but the residences nearest to such places are in greatest danger. The smaller and more compact the city or town, the more likely are malaria-transmitting mosquitoes to feed upon the inhabitants and to infect them.

In any malarious section, although there may be somewhat more malaria in the country, there are usually numerous cases among the inhabitants of the towns. Their frequent excursions into the country expose them to infection, and usually the poorly-kept town has many places favorable for the breeding of *Anopheles*. Although the towns are not as favorable for the growth of *Anopheles* as is the immediately surrounding territory, they are sufficiently favorable so that during a rainy spell or season, otherwise conducive to the growth of *Anopheles*,

numbers of this insect from the surrounding country overflow into the town and produce large numbers of progeny. Malaria is, however, a rural disease to such an extent that in the majority of instances if it were eliminated from the country it would naturally disappear entirely from the towns and cities.

(b) *Exposure to Hardship and Cold*.—Great hardship, violent exertion and exhaustion predispose to the development of clinical symptoms in already infected individuals. A surgical operation, for instance, or childbirth, is frequently followed by symptoms in those who have not exhibited symptoms for many months, although they may have been carrying the infection about all the time. This being the case, it is reasonably certain that certain conditions increase the susceptibility to infection as well. It is the author's opinion that an even, cold temperature reduces the susceptibility to malaria infection. It is also certain that infection is not likely to take place during cold weather.

(c) *Natives versus Newcomers and Immigrants*.—Persons who have lived in a malarious section for a long time and have had repeated attacks of malaria, especially during childhood, are less susceptible to infection and to the development of clinical symptoms than are newcomers and immigrants, especially those who have not thus acquired more or less resistance to the disease, or those from a non-malarious locality. Persons from non-malarious countries, on coming to a malarious region, develop clinical malaria more frequently than the natives, and they also have a much more severe type of the disease. This is especially true of adults.

(d) *Filth, Overcrowding, Bad Ventilation, Poor Lighting*.—Filth has nothing to do with the production and development of malaria except that persons who are careless as to cleanliness are much less likely to protect themselves against malaria.

Overcrowding would tend to increase the transmission of malaria in otherwise favorable localities.

Bad ventilation has nothing to do with the development of malaria or with its transmission, except that close quarters offer favorable resting and hiding places for *Anopheles*.

Poorly lighted or dark residences offer more favorable resting places and hiding-places for *Anopheles* than do well-lighted quarters. In this way they favor the transmission of malaria. There is a rather general opinion in much of the heavily infected malaria section of the United States that sleeping in well-lighted houses or keeping bright lights burning during the night tends to prevent malaria. There is possibly a certain amount of truth in this, for *Anopheles* do not venture into well-lighted houses and rooms as they do into dark ones.

(e) *Occupational Diseases*.—Occupation has no influence upon the occurrence of malaria except in so far as it may influence the exposure to infection or possibly to those hardships and other factors which tend to precipitate attacks in infected persons. It is true that individuals of the laboring class usually live in poorer houses and, especially, in houses which are poorly screened, if screened at all. This fact tends to

favor the transmission of malaria. Also, such individuals have not the same advantage of proper medical treatment, and therefore cannot overcome malaria infection to the same extent as those who can better afford proper medical attention.

Ignorance tends to increase the prevalence of malaria in two ways. Any person who is at all well informed knows that malaria is transmitted by mosquitoes and that it may be prevented by proper screening. The more ignorant class of people, on the other hand, do not realize and appreciate this to the same degree, and in fact do not screen their homes to the same extent, nor as effectively as do the better informed. In the light of our present knowledge as to the effectiveness of **quinin** treatment for disinfecting individuals affected with malaria, it seems that intelligent, well-informed individuals hardly deserve any sympathy if they have malaria. A man who lives in an intensely malarious section and who does not protect himself and family by properly screening his home, provided he can possibly afford to do so, shows himself to be extremely ignorant or neglectful of his own health and of that of his family.

(12) *Toxic Agents: Drugs, Dust, Fumes, Vapors, Gases, Acids, etc.*—These play no part in malaria.

(13) *Diet: Disorders of Metabolism.*—So far as any information at the author's disposal is concerned, no particular diet especially predisposes to malaria, although it would not be surprising to discover that diet does play an important part in the susceptibility to this and to many other diseases through its effect upon the natural or acquired processes of immunity. Overeating of indigestible food, such for instance as muscadines, watermelons, green fruit, etc., predisposes to the precipitation of attacks in individuals who are already infected, and in all probability also to increased susceptibility to infection in the event of inoculation.

(14) *Worry: Mental Shock.*—Great worry or mental strain tends to precipitate attacks in individuals who are already infected. Perhaps it may also render infection more likely in the event of inoculation.

(15) *Overexertion: Strain.*—Great physical strain or overexertion tends to precipitate attacks of malaria in infected individuals. An exertion approaching exhaustion is likely to precipitate attacks in malaria carriers who have perhaps escaped recognized clinical symptoms for many months.

(16) *Trauma.*—It frequently happens that following trauma involving considerable shock, malaria develops in persons who are already carrying the infection but have not active clinical symptoms. Surgical operations are frequently followed by the development of clinical symptoms of malaria in persons who have been previously infected but who show no clinical symptoms at the time. Childbirth is also frequently followed by the development of clinical malaria in infected women.

(17) *Imperfect Sewerage and Contaminated Water Supplies.*—It is not generally appreciated how great a factor imperfect water and sewerage systems are in the production of mosquitoes and thereby in

the transmission of malaria in small towns in malarial sections. This is especially true in those localities where artesian well water is used to any considerable extent.

The town of Ruleville in Sunflower County, Mississippi, which the author investigated in 1918, is an illustration of the way in which an imperfect water system may be responsible for a great deal of mosquito breeding. In this little town, not more than about half a mile square, which has a population of a thousand, at the most, eighty-nine different mosquito-breeding pools or accumulations of water due to leaking water pipes or hydrants were found. The water is supplied by flowing artesian wells and is inexpensive. There is no necessity to economize, and therefore a leaking water pipe or waste of water, unless the overflow is sufficient to produce great inconvenience to some one, does not attract attention and is not corrected. For months and years leaking pipes are allowed to leak, and it does not require a large amount of water to saturate the soil and finally form a pool. These pools are frequently more or less overgrown with grass and other vegetation and furnish ideal breeding ground for *Anopheles*. In Ruleville it was possible to prevent mosquito breeding almost entirely, simply by requiring that all leaking water pipes be repaired and that no waste water be allowed to accumulate and produce pools. There are hundreds of towns in the Mississippi Delta in almost the same condition. Most of the mosquito breeding that is going on is due to defective water pipes and sometimes also to defective sewerage and drainage. The overflow from septic tanks is frequently not properly taken care of, and although not likely to be a source of *Anopheles*, it may be a great breeding-place for other mosquitoes.

(18) *Pregnancy*.—There seems some difference of opinion as to whether pregnancy predisposes to attacks of malaria in otherwise infected individuals. Mannaberg⁴ says, "Pregnancy constitutes no protection against malarial infection, notwithstanding observations to the contrary. In a gravid woman the infection often takes a severe form." Abortions occur frequently and are due in all probability largely if not entirely to the localization of malaria parasites in the uterine vessels. These may be considered the exciting cause of the abortion. The danger of abortion is greater as the pregnancy advances. The fetus is usually dead in cases of abortion and frequently has been dead for several days.

It is important to know that malaria is very likely to give rise to abortion if not treated, because of the fact that with most of the laity the idea prevails that quinin is likely to produce it. It should be known that it is the malaria which produces the abortion in most cases in which it occurs following the taking of quinin for malaria, and not the quinin itself. There is much greater danger of abortion resulting from malaria than from the taking of quinin. There is, therefore, no question as to the proper choice in cases in which malaria and pregnancy co-exist. It is even more important to give quinin in cases of malaria accompanied by pregnancy than in others, because if not controlled the malaria is very likely to cause abortion and loss of life.

TABLE 1.—RECURRENT CASES OF ESTIVO-AUTUMNAL MALARIA PROBABLY NOT DUE TO RE-INFECTION. (*Craig*)

Case No.	Initial Attack	First Recurrence	Second Recurrence	Third Recurrence	Fourth Recurrence	Fifth Recurrence
1	Oct. 12	10 days	30 days	36 days		
2	Nov. 19	12 days				
3	Feb. 27	15 days	20 days	30 days		
4	Nov. 2	18 days	30 days	30 days		
5	Mar. 30	19 days	20 days			
6	Dec. 8	20 days				
7	Jan. 24	20 days	60 days			
8	Feb. 12	20 days				
9	Dec. 24	20 days				
10	Feb. 6	20 days	20 days			
11	Feb. 6	20 days	48 days			
12	Dec. 25	21 days	33 days			
13	Mar. 1	22 days				
14	Nov. 29	22 days				
15	Nov. 14	24 days				
16	Feb. 4	24 days	20 days	38 days	30 days	
17	Oct. 30	24 days	16 days			
18	Aug. 29	24 days	26 days			
19	Mar. 17	24 days				
20	Feb. 4	25 days	16 days	20 days		
21	Dec. 30	26 days	36 days	30 days	90 days	30 days
22	Jan. 26	26 days	48 days	90 days		
23	Jan. 11	26 days	22 days			
24	Oct. 2	27 days				
25	Nov. 2	27 days				
26	Mar. 2	27 days	52 days			
27	Feb. 5	28 days	21 days	20 days	21 days	
28	Dec. 12	28 days	28 days			
29	Oct. 29	29 days	48 days	15 days		
30	Jan. 17	30 days				
31	Jan. 1	30 days	30 days			
32	Jan. 10	30 days				
33	Jan. 20	32 days				
34	Oct. 19	33 days	26 days	90 days		
35	Jan. 19	34 days	40 days			
36	Oct. 18	34 days	50 days			
37	Jan. 25	34 days	26 days	17 days		
38	Oct. 21	36 days	56 days			
39	Feb. 30	36 days	66 days			
40	Aug. 13	36 days	35 days			
41	Nov. 27	36 days				
42	Sept. 1	37 days	49 days			
43	Oct. 18	38 days				
44	Oct. 17	38 days				
45	Aug. 13	38 days				
46	Sept. 6	41 days				
47	Oct. 31	42 days	20 days			
48	Jan. 1	45 days	30 days			
49	Nov. 3	46 days	21 days			
50	Dec. 7	49 days				
51	Feb. 24	50 days	24 days	41 days		
52	Oct. 24	51 days	39 days			
53	Jan. 18	61 days	153 days			
54	June 14	64 days	66 days	14 days	20 days	20 days
55	Mar. 3	80 days	120 days	96 days		

TABLE 2.—RECURRENT CASES OF TERTIAN MALARIA PROBABLY NOT DUE TO RE-INFECTION. (Craig)

Case No.	Initial Attack	First Recurrence	Second Recurrence	Third Recurrence	Fourth Recurrence	Fifth Recurrence
1	Nov. 2	16 days	21 days
2	Aug. 4	18 days	20 days
3	Aug. 28	19 days	30 days	26 days	46 days
4	Nov. 6	20 days	24 days
5	Jan. 17	20 days	32 days	30 days	24 days
6	Nov. 23	21 days	20 days	26 days
7	Oct. 6	21 days	30 days
8	Sept. 17	21 days	22 days	27 days
9	Aug. 27	22 days	36 days
10	Feb. 12	22 days	18 days	16 days	27 days
11	Jan. 17	27 days
12	July 20	30 days
13	May 3	30 days
14	Nov. 1	30 days
15	Sept. 22	33 days
16	Sept. 1	37 days
17	Dec. 13	38 days
18	Sept. 22	41 days

(19) *Previous Attack*.—Whether or not an attack of malaria will be followed by relapses or subsequent attacks will depend largely upon the treatment the patient undergoes. If thorough treatment is given, so that the patient is disinfected, an attack is not followed by subsequent recurrences except in cases of re-infection. If, on the other hand, the treatment is not sufficient to disinfect the patient, there is great probability of a relapse. The frequency of malaria relapses is very much greater than it is generally supposed to be. Tables 1 and 2 are taken from Craig's "The Malarial Fevers" and represent cases of malaria in which re-infection was considered at least very improbable and which are therefore reasonably certain to be relapses. Craig says that all of them received thorough quinin treatment during the active symptoms and that most of them received prophylactic quinin once a week. It is noteworthy that, in the case of tertian malaria, those who had their first recurrence after the twenty-sixth day never had subsequent recurrences. It is possible, however, that the small number of the cases examined may cause this apparently striking difference.

In the author's investigation of malaria in Sunflower County during 1918, conclusive evidence was obtained that at least 37 per cent. of the individuals who have attacks of malaria during a given year will also have attacks during the following year, independently of re-infection.

James⁵ says that in 1911 the Department of Sanitation of the Isthmian Canal Commission sent out to authorities on malaria in different parts of the world a circular letter in which information was requested as to the amount of malaria due to relapse and to other

factors. Practically all the authorities referred to agreed in stating that a very large proportion of malaria, from 50 to 90 per cent., in malarious communities, is due to relapse.

An analysis of the data in the Sunflower County studies of 1918 shows that more than 50 per cent. of the attacks of malaria occurring during a given year in that locality are relapses. A fuller discussion of these observations will be found in the Osler Anniversary Volume.⁶

(20) *Chronic Alcoholism*.—Chronic alcoholism tends to increase the probability of attacks in infected individuals. Alcoholism also tends to increase the probability of the occurrence of pernicious malaria.

(21) *Association with Other Diseases*.—Malaria may be associated with any other disease. There is no disease which prevents the occurrence of malaria. On the other hand, a good many of them tend to increase the susceptibility to clinical attacks of malaria in infected persons. Anything that lowers the general vitality of the individual increases his susceptibility to attacks of malaria. Debility, chronic disease, cachexia and allied conditions, focal infections, etc., all increase the susceptibility to attacks of malaria, provided always the malaria parasites are present.

2. EXCITING CAUSE: THE MALARIA PARASITE.—A. *Morphology and Development*.—The parasites of malaria are organisms belonging to the division *Protozoa*, class *Sporozoa*, order *Hæmosporidia*. There are three varieties: *Plasmodium malariae* (the quartan parasite), *Plasmodium vivax* (the tertian parasite), and *Plasmodium falciparum* (the estivo-autumnal parasite). There are at least two and probably more subdivisions of the estivo-autumnal parasite. Whether these are truly different parasites or whether they are simply widely differing strains of the same parasite cannot be stated definitely at the present time. A majority of students believe that there are at least two different parasites—the quotidian estivo-autumnal and the tertian estivo-autumnal. They are similar, however, in most respects and for all ordinary purposes there is no great need for differentiation.

(a) *The Life Cycle of Malaria Parasites in Man*.—The life cycle of malaria parasites in man is of much importance and interest. Although there are at least three distinct parasites, they all live, grow and reproduce in the body of man in very much the same way. We can therefore conveniently describe this life cycle and then take up the separate descriptions of each one of the parasites: The youngest form, the merozoite, consists of a mass of protoplasm containing a nucleus which is quite rich in chromatin. The merozoite as set free by the segmenting schizont has one flattened side and one round or oval side. It is rather cup-shaped. The nucleus is situated more or less toward the periphery. Under favorable conditions the merozoite fastens to an erythrocyte, the flat side always against the erythrocyte. On account of the clear, non-staining vacuole which the parasite contains at this stage, it appears in stained specimens to be ring-shaped. It is frequently spoken of as a *signet ring*.

As time progresses the parasite grows, becoming larger and larger



SCHIZONTS

GAMETES

QUARTAN MALARIA PLASMODIA

(*Plasmodium malariae*)

(By permission of Drs. Bass and Johns, of New Orleans, and Rebman Company,
of New York)

until in twelve or fifteen hours, in most cases, an examination of fresh preparations of blood shows one or more small, brownish, dancing pigment granules in the parasite. In the case of the tertian parasite and also of certain strains or divisions of the estivo-autumnal, the parasite is quite ameboid. The quartan parasite and others of the estivo-autumnal type are only slightly ameboid. In most ameboid specimens the parasite projects pseudopodia into or perhaps to the surface of the erythrocyte and presents the greatest multiplicity of figures. In living specimens, with suitable illumination, one may see the greatest activity of the protoplasm, not only in its movement through or on the erythrocyte, but also in the mass itself, as evidenced by the dancing of the pigment granules. Apparently the substance of the erythrocyte is consumed as the parasite grows, and no doubt serves as part, at least, of the latter's nutriment. The hemoglobin of the erythrocyte is broken up into globin and hematin and the latter goes to make the pigment granules.

In from twelve to twenty-four hours the nucleus becomes polymorphous and begins to divide. It was formerly thought that division of the nucleus did not take place until the full maturity of the parasite, but such is not the case, as anybody can observe by following the development of the parasite in cultures. As the development advances the pigment increases in amount, and soon after the middle of the developmental period is passed it begins to collect in a mass in some part of the parasite. Usually the tendency is for it to collect about the center, but often it is also found nearer the periphery. Formerly the pigment granules were rather widely scattered throughout the protoplasm of the parasite. Long before full maturity has been reached, especially in estivo-autumnal parasites, these pigment granules have all collected in a single compact mass, and they attract attention, in fresh specimens, to the presence of the parasite.

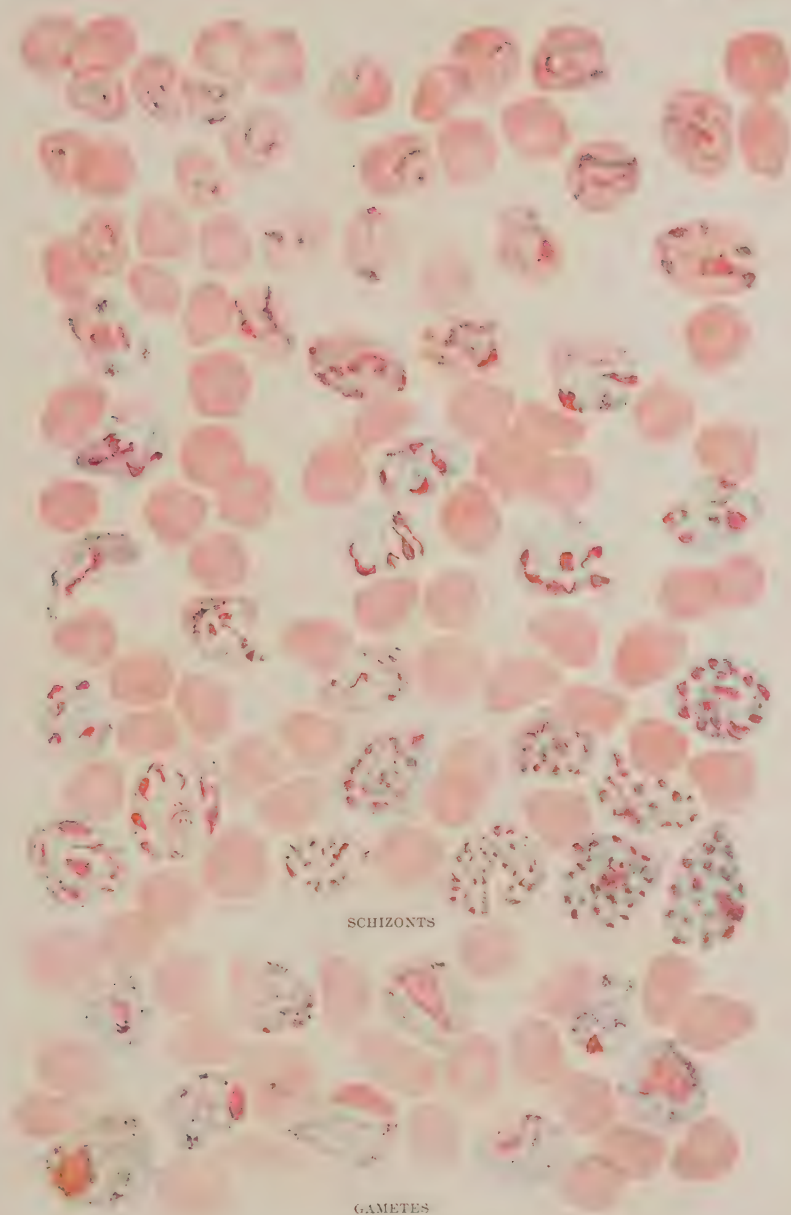
Although the division of the nucleus is going on all the time after the middle of the developmental period, there does not seem to be any division of the protoplasm until toward the last of the period. The developmental period varies from about thirty hours to seventy-two hours in artificial cultures. It probably varies in this same way in the tissues of man. When full maturity is reached the parasite occupies a large part of the remaining erythrocyte. Most of the erythrocyte has been consumed, leaving little more than a thin shell or capsule containing the fully developed parasite. Suitably prepared specimens at this stage show that not only has the nucleus divided into a variable number of small nuclei, but that the protoplasm has also divided so that now each small division of nucleus is accompanied by its own division of protoplasm. We have, in fact, a capsule containing a number of young malaria parasites, the result of segmentation of the original parasite. This division by segmentation without sexual influence is known as schizogony and parasites which divide and develop asexually in this way are known as schizonts. There is some difference in the use of the term, some authorities calling only the fully developed and segmented parasites schizonts, whereas others call them schizonts at any

stage of their development. The author's impression is that all asexual parasites should be called schizonts.

At about this time the capsule containing the fully developed and segmented parasite ruptures, setting free its contents, consisting of the young parasites, now merozoites, the pigment granules and other material contained within the capsule. Each merozoite is capable, if conditions are favorable, of attaching itself to another erythrocyte and passing through a similar cycle of development, giving rise in turn to another crop of merozoites which may continue the process. Fortunately, most of the young parasites produced are destroyed by the protective agencies of the body. Generally they are phagocyted by the endothelial cells lining the capillaries in which the process takes place. The large mononuclear leukocytes phagocyte and destroy many of them. It is not certain what part the blood-plasma may play in their destruction. In artificial cultures the young merozoites cannot withstand the action of blood-serum for any length of time. They are very promptly affected, so that they do not take the stain in the normal way and are apparently killed. We have never been able to grow merozoites that have been exposed to the action of serum in the culture.

(b) *Segmentation Taking Place Especially in the Capillaries.*—The general impression is that malaria parasites live, grow, develop and reproduce in the blood stream. As a matter of fact, nothing of the sort occurs. It is true that young parasites are present in the blood stream at almost all times and also that ameboid parasites appear and reappear in the circulating blood in individuals suffering from malaria. In fact, a large part of the life cycle of the parasite is spent lodged in the capillaries of different organs and tissues, particularly in the bone marrow, spleen, etc. Estivo-autumnal parasites disappear from the peripheral circulation by the time they have reached one-fourth their full size and do not reappear at all, except inasmuch as the merozoites produced by segmentation may appear attached to other erythrocytes as young parasites. As soon as those parasites which have little ameboid motility reach such a size that they cannot adapt themselves so as to pass through the narrow places in the capillaries, they lodge and remain there for the remainder of their developmental period, which, as just stated, is about three-fourths of the entire life period. It is very probable that the merozoites that do succeed in attaching themselves to erythrocytes do so before they are dislodged from the capillaries in which they were produced.

The more ameboid parasites, as, for instance, the tertian, are capable of moving and changing their shape in such a way as to pass through the capillaries very much as leukocytes and erythrocytes do, and this is the explanation for the fact that parasites in all stages of development may be seen in the peripheral blood. It must never be thought that anything like all of the parasites in the body of an individual are present in the circulating blood. In reality, the large parasites that are seen are simply overflow, or parasites that have accidentally passed through the capillaries. One cannot gain a correct idea of the number



TERTIAN MALARIA PLASMODIA
(*Plasmodium vivax*)

(By permission of Drs. Bass and Johns, of New Orleans, and Rebman Company,
of New York)

of parasites present in an infected individual by noting the number of parasites in the circulating blood.

(c) *The Tendency of Malaria Parasites to Reproduce by Crops.*—

There is a tendency to reproduce by crops on the part of all species of malaria parasites. This tendency, however, is very much more marked in the case of the tertian and quartan than in the estivo-autumnal type. In the tertian the cropping is almost always sufficiently definite to give rise to the characteristic intermittent fever. Usually if we examine a blood specimen from a case of tertian malaria we will be able to recognize that almost all of the parasites are of approximately the same size and age, or, in instances of two different sizes and ages, one approximately twenty-four hours older than the other. As a result of this tendency to development by crops, almost all of the parasites in a given infection segment at about the same time of day. Those that have grown a little faster seem to slow down their growth as they approach maturity and those that are behind hasten and catch up. It is believed that almost all the parasites segment within a comparatively short time, perhaps only a few minutes. In cases in which there are sufficient parasites to give rise to clinical symptoms, there are countless millions of parasites present, each one of which sets free from the capsule within which it developed whatever toxic or harmful material it contains. There is a difference of opinion as to whether or not any toxin is produced, but there is certainly something that has a definite effect upon the system. Whether that something is in the nature of a toxic substance or whether it is the effect of a foreign protein, as suggested by Vaughan, or whether it is due to the effect of the pigment, as suggested by Brown, is not known.

The first effect of the segmentation of a crop of parasites of sufficient number is to cause a general relaxation of the entire vascular system, resulting in the accumulation of the blood in the large vessels, and in the organs and tissues of the body where there is least pressure upon the blood-vessels. The result of this is that very little blood passes through the surface of the body and that therefore it is not kept warm and tends to assume the temperature of the surrounding air. The patient has a chill which lasts a variable length of time, depending upon the amount of toxin produced, the length of time required to eliminate or neutralize it and perhaps upon other factors which we do not at present understand. The symptoms and the manner in which they are produced are discussed at greater length in another chapter.

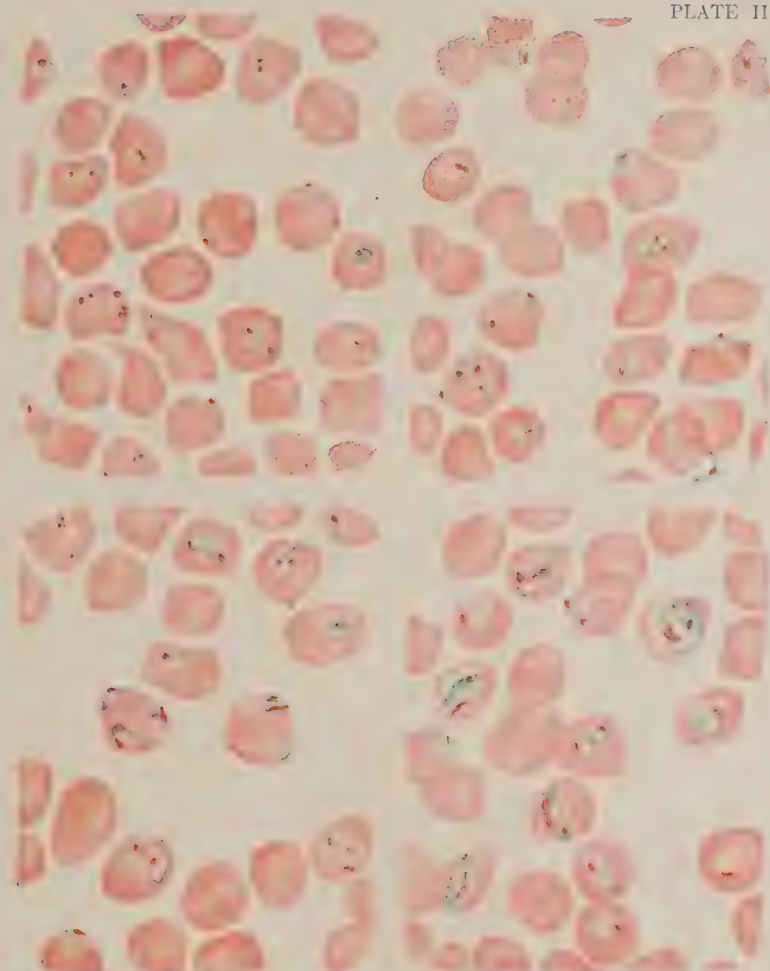
The crop of merozoites produced at the time of segmentation in a given case will mature and segment again in forty-eight hours in the instance of tertian and estivo-autumnal and in seventy-two hours in the case of quartan. If two crops of parasites are present, there is segmentation on each day, giving rise to the quotidian chill and fever: but it must be fully understood that this represents two infections and two cases of malaria in the same individual.

Asexual reproduction, such as has been described, may go on for several weeks, and if the resisting agencies of the individual are not

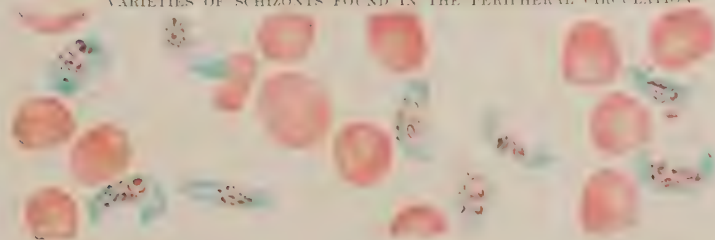
sufficient to prevent it, the patient is finally destroyed. In most instances the destruction results from the obstruction of the capillaries of vital organs and tissues of the body, producing what is rightly called pernicious malaria. In pernicious malaria the capillaries of vital organs, such as the brain, liver, kidneys and digestive system, are obstructed with so many parasites that there is not sufficient circulation to support the tissues and the functions of the organs. The preponderance of parasites obstructing the capillaries of one organ or another gives rise to the different clinical types of pernicious malaria. For instance, "cerebral malaria" is due to the localization of large numbers of parasites in the capillaries of the brain.

(d) *The Development of Sexually Differentiated Parasites.*—If an individual has had clinical malaria for ten days or two weeks, we are able, on careful examination of the blood, to recognize not only these asexual parasites, which have just been described, and which grow, develop and segment, giving rise to the clinical symptoms of malaria, but also a few or sometimes many other parasites which are different from these schizonts and which are known to be sexually differentiated. Those who are familiar with them are able to recognize and differentiate the male and female parasites. As they develop, instead of their nucleus becoming polymorphous and finally dividing, it remains single. These sexually differentiated parasites are known as macrogametocytes and microgametocytes, both commonly called gametes. Tertian and quartan gametes are sufficiently ameboid to enable them to pass through the smaller capillaries and therefore to appear and reappear in the peripheral circulation. The gametes of estivo-autumnal malaria are long, slender, and crescent-shaped, and show very little ameboid ability. Their size and shape permit them also to pass through the smaller capillaries and to appear and reappear in the peripheral circulation. The gametes of tertian and quartan malaria are round or oval and possess considerable ameboid ability, which facilitates their passage through the capillaries.

(e) *Parthenogenesis.*—There is considerable difference of opinion as to whether or not gametes are capable of reproduction in the body of man. It is certain that they do not reproduce sexually. There are, however, a good many students of malaria who believe that they do reproduce under special conditions by parthenogenesis. Craig has been an especially strong advocate of this view. By parthenogenesis is meant reproduction by female parasites somewhat like that which takes place in schizogony in asexual parasites, but without sexual influence. The author does not particularly favor the idea of parthenogenesis of malaria parasites: first, because parthenogenesis is not necessary to explain recurrences, more improved methods of examination having demonstrated that there are usually a few asexual parasites present for long periods after clinical symptoms have ceased; second, because, in artificial cultures in which only schizonts were present, pictures have been observed which resemble what has been considered to be parthenogenesis. The author does not feel prepared to state emphatically that partheno-



VARIETIES OF SCHIZONTS FOUND IN THE PERIPHERAL CIRCULATION



GAMETES

ESTIVO AUTUMNAL MALARIA PLASMODIA
(*Plasmodium falciparum*)

By permission of Drs. Bass and Johns, of New Orleans, and Reiman Company,
of New York)

genesis does not take place, but he does not consider that the evidence is sufficient to warrant the statement that it does.

(f) *Exflagellation of Gametes*.—If we draw blood containing gametes and treat it in some manner as, for instance, by adding a little water or preferably a hemolytic fluid, so as to damage or partially or completely dissolve the erythrocytes, the gametes quickly take on a new activity. The microgametocyte, the male gamete, becomes round or oval, and if we observe favorable specimens we may note bulging and ameboid activity at the periphery. Within a very short time, a few minutes only, such a parasite will project long, thin threads of protoplasm, usually from four to six in number, which lash about vigorously, moving the whole parasite, which whirls about. Sooner or later these threads break off and continue their movement. They are able to move rather rapidly through the plasma and are soon found at considerable distances from the parent parasite. After the several threads, now known as microgametes, have been thrown off, the microgametocyte dies and loses its normal staining reaction. The microgamete, if stained, is seen to contain a considerable filament of nuclear material, as well as the protoplasm.

Under favorable conditions the microgamete comes in contact with a macrogamete, or female parasite; it has been observed to enter and apparently to be swallowed up by the latter. There is union of the nuclear elements of the two cells, and the fertilized macrogamete becomes a zygote. The zygote becomes actively ameboid and is capable of passing through narrow spaces. It also begins to grow rapidly. The process that we have just described may be observed up to this stage under the microscope, in suitably prepared material. It has not been followed beyond this, although in artificially cultivated material the author has observed zygotes as much as four days old still alive. The author has never made any great effort to cultivate this sexual cycle of the parasite nor is he familiar with any of the work performed by others with this object in view. There is no doubt that the sexual cycle of malaria parasites can be cultivated whenever suitable technic is employed.

(g) *Sexual Development in Mosquitoes*.—If blood containing gametes is drawn, under favorable circumstances, by certain species of *Anopheles*, the sexual activity just described takes place and goes on to completion. The fertilized zygote in the stomach of the mosquito passes by means of this increased ameboid activity through the stomach wall between the cells and lodges on the surface of the stomach. Just how it is held in place we do not know, but it seems to be fairly firmly attached. Here continued growth and development take place. A thin cyst is soon formed and the parasite is now called an oöcyst. Its nucleus divides into a large number of daughter nuclei around each of which the protoplasm gathers, forming sporoblasts which are somewhat bound together. The nucleus of each sporoblast divides into a large number of small nuclei. These travel to the periphery and project somewhat. Finally they form very small spindle-shaped bodies, each consisting of

a comparatively small amount of protoplasm and a nucleus. These are known as sporozoites. This development requires a period of from about fifteen to twenty-five days in mosquitoes kept under artificial conditions. The temperature at which they are kept has a great deal to do with the rate of development. They develop very slowly at low temperatures and very much more rapidly at high temperatures.

When the period of full development has been reached, the oöcyst ruptures, setting free into the coelom, or abdominal cavity, of the mosquito a large number of sporozoites which are carried in some way, probably by the circulatory system of the mosquito, to all parts of the insect. Some of them reach the salivary gland, which seems to be especially inviting for them to collect in. In suitable preparations the sporozoites appear to be not only in the tubes of the glands but in the gland-cells themselves. Here they remain for quite a long time unless expelled by their host in drawing blood. It has not been definitely determined just how long they can live in the glands of the mosquito host, but it is quite certain that they may pass a dormant period, perhaps as long as the life of the mosquito itself. In the infected mosquito many cysts may develop, giving rise to a very heavy infection of the glands. On the other hand, the infection of the glands may be much lighter when only one or two or a few zygotes develop.

(h) *The Way in Which the Mosquitoes Inject Sporozoites.*—The food of mosquitoes is not blood, as is generally supposed, but plant and fruit juices and vegetable material entirely. The male mosquitoes do not draw blood and the females do so only for purposes of reproduction. Whenever the female mosquito reaches the stage of development at which she should produce eggs, corresponding to puberty in higher animal life, there develops a desire or call for blood from which to grow eggs. Eggs will not develop in a mosquito fed only on the normal food. They will only develop after she has obtained animal protein. When this development has been reached and the desire or call is present, the mosquito starts in search of a blood-meal and will draw blood from almost any animal she finds, including man. If she draws blood from a man whose blood happens to contain malaria gametes, she becomes infected. After she obtains a blood-meal, the ova rapidly develop and sooner or later the period is reached at which she should deposit the eggs in a locality favorable to their development. She usually goes to the same breeding-ground where she herself grew and deposits the batch of eggs.

Later there is another call for blood from which to develop another batch of eggs and she goes in search of blood again, usually in the same direction and to the same locality from which she obtained blood at first. If the period between the first feeding and the next feeding has been sufficiently long for the parasites to develop and produce sporozoites and for them to reach the salivary glands, she is now capable of transferring the infection to the individual from whom she draws blood.

The blood-collecting organ, or bill, of the mosquito consists practically of a hollow needle. This needle is stuck into the skin, but in order to draw blood it is necessary that it should enter a small blood-vessel. Normally

the blood-vessels are so small that it is difficult to enter them. Nature has provided this and all other blood-sucking insects with a secretion of the salivary gland which causes dilatation of the blood-vessels, or hyperemia. The mosquito first sticks her bill into the skin and then, by means of powerful muscles surrounding the salivary glands, forces some of the juice into the tissues. This causes dilatation of the vessels and usually the mosquito soon succeeds in entering a blood-vessel with her needle. Incidentally, if she has malaria sporozoites in her glands at the time, they are forced into the tissues and probably also into the blood-vessels, and the individual is infected.

It may be interesting to note that once the bill is in the blood-vessel, the mosquito is able to draw blood not by sucking, as is generally supposed, but by swallowing it as it is carried into the esophagus by capillary force.

Sporozoites introduced into the blood or into the tissues are capable of attaching themselves to erythrocytes. Perhaps they penetrate them promptly, but at any rate, they soon assume a round or oval shape, resembling merozoites produced by schizogony. They now develop in the same manner in which asexual parasites do—segment, and give rise to merozoites which continue the process of schizogony. In this manner and in this manner only are malaria parasites carried from one individual to another. The process just described applies to all species of malaria parasites.

(i) *Special Considerations.*—After having described the malaria parasites in general, it will now be advantageous to take up special considerations of the different species.

(1) *The Tertian Parasite.*—The merozoites of tertian parasites are about two microns in diameter. They cause rapid swelling of the host cell so that sometimes by the time the parasite is twenty-four hours old the cell is twice the diameter of normal cells. Not only does the cell enlarge but it becomes quite pale, apparently out of proportion to the enlargement. The paleness cannot be explained entirely by swelling. Specimens stained with any of the modifications of the Romanowsky stain show the presence of Schüffner's granules throughout the cell. These granules are not found in cells infected with any other malaria parasite. The parasite remains ring-shaped only a very short time, so that in practical examinations of ordinary blood preparations one seldom sees many rings. Ameboid activity begins early and is very marked. As soon as pigment is formed examination of suitable fresh blood preparations shows that it is very actively motile. It is also strikingly fine compared with the pigment produced in either quartan or estivo-autumnal parasites. The full-grown parasite is as large as, and sometimes larger than, the normal erythrocyte. All stages of the development of the parasite may be seen in the peripheral circulation, but there are only a few rosettes and parasites present as compared with the total number present in the organs and tissues in which the development is going on most extensively. The gametes are round or oval and their pigment is generally distributed throughout the protoplasm of the parasite.

(2) *The Quartan Parasite*.—The merozoites of quartan parasites are perhaps slightly smaller than those of the tertian type and they remain ring-shaped considerably longer. Usually a good many of them develop in from twenty-four to thirty-six hours in the form of bands across the erythrocyte, instead of showing the usual irregular shapes. In fact, the quartan never displays anything like the great irregularity of shape that is shown by the tertian. As the parasite develops the erythrocyte shrinks and its color intensifies. Pigment appears in from twenty-four to thirty hours and is coarser than in the tertian. It is also very much less active than in the tertian. The parasite matures in seventy-two hours and divides into not more than eight segments. All stages of the parasite appear in the peripheral circulation, but they become less numerous as they grow older. However, rosettes are frequently found in the peripheral blood. The gametes are round or oval and usually not numerous.

(3) *The Estivo-autumnal Parasite*.—The youngest merozoites in most cases of estivo-autumnal parasites are very much smaller than those of tertian or quartan. They consist of a chromatin granule and a very small ring. Sometimes there are two chromatin granules. These rings are frequently so small they are overlooked, especially by those who are not well trained and have not good staining technic. Only these small ring forms and perhaps gametes are seen in the peripheral circulation. These parasites, as they grow in artificial cultures, never reach more than about half the diameter of erythrocytes. In artificial cultures they reach full maturity in from thirty-six to forty-eight hours, and they produce apparently only about sixteen segments. These parasites have extremely little ameboid activity, which is believed to explain their disappearance from the circulation while they are small. Preparations made from half-grown or older parasites in artificial cultures, by placing a drop of the material containing them on a slide, covering it with a cover glass and then examining it under the microscope while pressing upon the cover glass, show that they are more resistant and unyielding to pressure than any of the other parasites. One gains the impression that they would not yield and mold their shape in order to pass through narrow places in the capillaries. The gametes are crescent-shaped and are to be found in the peripheral circulation.

In other specimens of estivo-autumnal parasites the merozoites are as large as those of tertian, and frequently the ring of protoplasm is considerably thicker and heavier. The definite signet ring is not present to the same extent as it is in the first form of the estivo-autumnal type. A tendency to ameboid changes is shown, but usually the parasites disappear from the circulation before this is very marked. They spend from eight to twelve hours of their forty-eight hour life period in the peripheral circulation, and the balance of the time they are lodged in the capillaries of different organs and tissues. In artificial cultures parasites do not show a great deal of ameboid change, and they finally develop to almost the diameter of the host cell. They often produce twenty-four or more merozoites in artificial cultures. This is the form which is gen-

erally called malignant tertian, the other one just described being commonly called quotidian. In artificial cultures the pigment is coarse and soon collects in a mass in some part of the parasite. The gametes are crescent-shaped and usually show very little of the remaining erythrocyte from which they developed.

The differentiation of the different varieties of malaria parasites will be aided by reference to the colored plates (Plates I, II and III) and to Table 3, taken from Bass and Johns' Laboratory Diagnosis:

TABLE 3.—DIFFERENTIATION OF MALARIA PARASITES

	Estivo-autumnal	Tertian	Quartan
Schizonts in the peripheral blood.	Rings only.	All sizes.	All sizes.
Shape of gametocytes.	Crescentic and oval.	Round or oval.	Round or oval.
Shape of outline of schizonts in peripheral blood.	Rings. May have two chromatin granules.	Irregular after ring stage is passed.	Regular after ring shape is passed.
Influence upon color of erythrocyte.	Not changed.	Faded, pale.	Darker. Normal red color intensified.
Influence upon size of erythrocyte.	Not changed.	Enlarged.	Reduced.
Pigment in schizonts and gametocytes.	Medium to coarse.	Very fine.	Coarse.
Schüffner's granules.*		Often present.	Not present.
Number of segments in rosette.		32.	8.
Period of asexual development.		48 hours.	72 hours.

*Red-staining granules in the erythrocyte containing the parasite.

B. *The Distribution of Malaria Parasites in the Body.*—It is generally supposed that malaria parasites are distributed in the circulating blood. It is true that there are some parasites present in the blood of almost all individuals who are infected but, as a matter of fact, these are either overflow parasites or those which have escaped from the capillaries temporarily as a result of ameboid activity or because of their small size or special form, as, for instance, in the case of the estivo-autumnal gamete. Probably the bone-marrow contains more malaria parasites than any other part of the body, in ordinary cases; the spleen comes next, the liver perhaps next and then come such organs as the brain, gastrointestinal canal, hematopoietic glands, etc. In pernicious malaria the number of parasites present in vital organs and tissues is frequently enormous. In many such cases even the capillaries of the skin contain large numbers. The pigment held in the capillaries of the skin is sometimes sufficient to give a pigmented or brownish yellow appearance.

C. *The Cultivation of Malaria Plasmodia.*—The first successful cul-

tivation of malaria plasmodia *in vitro* was announced by Bass⁷ in 1911. The technic was not given and, as a matter of fact, only partial success had been attained. In 1912 Bass and Johns⁸ published the technic, and in September, 1912, exhibited cultures of plasmodia at the International Congress of Hygiene and Demography in Washington. These were observed by hundreds of scientists from different parts of the world and recognized by all familiar with malaria plasmodia to be genuine and to represent every stage of reproduction of the parasite by schizogony. A still more complete description of the technic, in which every detail was covered, was published by Bass⁹ in 1914.

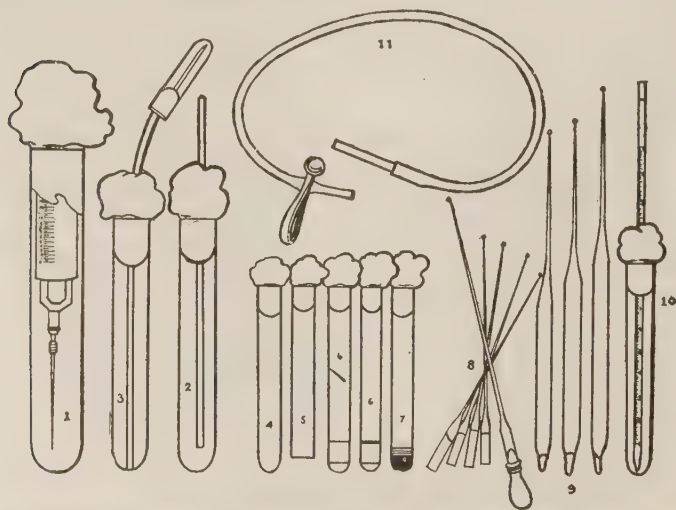


FIG. 6.—APPARATUS USED IN CULTIVATION OF MALARIA PARASITES. (Bass, American Journal of Tropical Diseases.)

Since the author's first publication of the technic, malaria plasmodia have been cultivated by different workers in almost every civilized country. They have been grown only in human blood. Success depends upon the presence of a suitable quantity of dextrose in the culture. So far as the author is informed, no successful cultivation has been accomplished without the use of the dextrose.

The following is the original *technic*, taken from the *American Journal of Tropical Diseases and Preventive Medicine* (1914, i, No. 8, 546).

"Apparatus and Materials Required.—One generation of parasites may be grown with very simple technic, but they are destroyed soon after segmentation, and often just before, by the leukocytes in the blood from the patient. The apparatus needed for the cultivation of one generation only of parasites are the following:

"1. Syringe and needle. An all-glass syringe, capacity 20 c.c. (or

10 c.c.), graduated, is convenient for this purpose. Syringes with rubber, leather or cotton plungers, washers, connections, etc., are not serviceable because they cannot be easily cleaned after being used, and when they are sterilized they give off substances which are harmful to malarial plasmodia. A coarse needle is necessary because strong force or strong suction so alters the cells (or parasites) that the parasites die in a short time. Such a needle is also desirable to avoid leaking and bubbling of air into the syringe and to facilitate taking blood into it and expelling it from the syringe.

"2. Defibrinating tube. Tubes $2\frac{1}{2}$ cm. in diameter and of whatever length will be accommodated by the centrifuge (if a centrifuge is to be

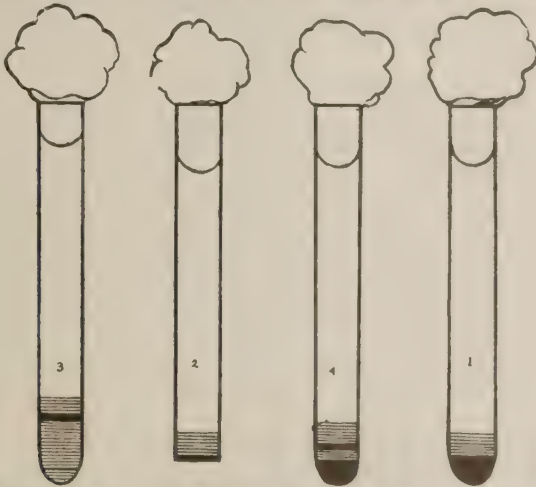


FIG. 7.—DIFFERENT FORMS OF MALARIA CULTURES. (Bass, American Journal of Tropical Diseases.)

used) are appropriate. This tube is plugged with a cotton plug having a plain glass rod (0.5 cm. diameter) running through it and extending to the bottom. A glass tube may be substituted for the glass rod, in which case the outer end is connected to a needle by means of a short rubber tube (Fig. 1, 3). More recently this rubber connection has been dispensed with and the needle (barrel without any shoulder) is welded into the tubing. Platino-iridium needles are necessary for this purpose. Blood is collected directly into the defibrinating tube by sticking the needle into a distended vein.

"3. Culture tubes not less than 1.25 cm. in diameter by 12.5 cm. deep.

"4. Graduated pipet, 1 c.c. graduated in hundredths.

"5. Dextrose (Merck's) 50 per cent. solution in water. This should be sterilized at 100° C. on three consecutive days.

"6. Capillary pipets. Glass tubing 0.5 to 0.6 cm. in diameter is

the proper size from which to make these pipets. The capillary should be rather coarse since fine capillaries are destructive to malarial plasmodia. The large end of these pipets should be plugged with cotton before sterilizing.

"7. Rubber bulb. This should be of the best quality and fit the pipets well. The delicate uses to which the pipets are placed require perfectly fitting bulbs.

"8. Incubator regulated to a temperature of 40° C. It is possible to use an incubator running as low as 38° C., and in fact, often the parasites grow fairly well at 37° C.

"The following apparatus will be required if more than one generation of parasites is to be grown, or if it is desired to avoid the dead parasites which are present in the deeper layers of cultures containing a thick column of cells.

"9. Centrifuge, speed 800 to 2000 r. p. m. Higher speed centrifuges are likely to be destructive to the parasites or at least to cause such changes in the cells as to disfavor their growth.

"10. Culture tubes 1.25 cm. by 12.5 cm., with flat bottom or with disk of pure white filter paper supported 1.25 cm. or more from the bottom of the tube by a piece of glass tubing. The latter should be cut straight across and should fit the culture tube fairly closely.

"11. Plain pipets, capacity 5 to 20 c.c. These pipets should be plugged with cotton before sterilizing and the small end (large capillary) should remain hermetically sealed until it is to be used. They are not used a second time.

"12. Rubber tube 50 cm. long, mouth piece and pinch cock. This tube should be of proper size to fit the neck of the large pipets just described.

"The syringes, tubes and pipets must be sterilized in the dry sterilizer. A few drops of water in a tube in which blood containing plasmodia is placed will usually cause the death of the parasites. The dry sterilization must not be carried to the extent of scorching the cotton plugs, for the smoke that condenses on the inner surfaces of the tubes is sufficient to kill all the parasites in a culture.

"*Technic for Cultivating One Generation Only of Parasites.*—Blood is collected from the patient's vein at the bend of the elbow. If drawn with the syringe it is expelled directly into the defibrinating tube. The latter should be tilted to one side and care should be taken to avoid unnecessary exposure of the blood to the air. In either case, 1/10 c.c. of the 50 per cent. solution of dextrose for each 10 cubic centimeters of blood to be taken is placed in the defibrinating tube before the blood is drawn. Defibrination is effected by gently stirring or whipping with the rod or tube which extends through the cotton plug. The whipping in of air, causing bubbles, must be avoided. The plug and rod may now be replaced by a plug from another tube of the same size.

"This defibrinated dextrose blood containing malarial plasmodia may be transferred to other tubes or incubated in the original tube. In any event the column of blood must be 2.5 to 5 cm. deep. This gives a

column of serum 1.25 to 2.5 cm. deep above the cells and parasites when the latter have settled. Supernatant serum more than 2.5 cm. deep has no advantage. When this is less than 1.25 cm. deep the parasites often die before segmentation occurs. We have occasionally seen perfect segmentation, however, under 0.6 cm. of serum.

"The parasites live and develop at the top of the column of precipitated cells in a layer varying in thickness from 0.05 to 0.1 cm. All parasites beneath this layer die in from two to twenty hours; the time depends upon factors which have not been determined. Some grow considerably before they die and we have occasionally seen small ring forms attain over half the full adult size in the deep part of the cell mass. When parasites die in these deep cells the central clear space in the small ring closes, or if the parasite is older the irregular projections, pseudopodia, are withdrawn. If pigment is present it loses its motility. The protoplasm gradually shrinks, losing its staining reaction, and finally only the nuclear chromatin granule remains. This also stains poorly. In the instance of very small parasites often the red blood-cell shows little or no evidence of the previous presence of the parasite. This suggests the possibility that the young parasite had not yet entered the cell substance.

"The parasites in the thin layer at the top of the column of cells develop and may be examined at any time by drawing a small quantity of cells from this layer by means of a capillary pipette. Some considerable practice is required in order to do this without drawing cells and dead parasites from just beneath this layer. The pipet may be passed through a flame to sterilize it on the outside, but it must be allowed to cool thoroughly before it is used, since, in our experience, a temperature of 45° to 50° C. kills the parasites in a very short time.

"Such a temperature also alters the red blood-cells in some way so that they are rendered permeable to the surrounding serum, and this effect is destructive to the parasites. Great care must be taken in handling tubes containing cultures to keep them in an upright position. Tilting to the side results in burying and killing the living parasites in the thin layer at the top of the column of cells. With sufficient care a sample may be removed from the culture and the tube be returned to the incubator without killing the parasites. This may sometimes be repeated several times.

"*Technic for Cultivating More Than One Generation of Parasites.*—If more than one generation of plasmodia is to be cultivated, it is necessary to remove the leukocytes at the time the culture is made in order to avoid destruction of the parasites by them at the time of segmentation. The infected blood from the patient is centrifugalized sufficiently to force the leukocytes to the surface of the cells. The length of time necessary to centrifugalize varies with the speed, length of arm, etc., of the particular centrifuge used and should be determined by experiment. Unnecessary centrifugalization should be avoided.

"The supernatant serum is drawn off and put in culture tubes. The column of serum in each should be 1.25 to 2.5 cm. deep. Cells and

plasmodia are carefully drawn from about the middle of the centrifugalized cells and planted at the bottom of the serum in the culture tubes. Flat-bottom tubes are an advantage. 1/10 to 2/10 c.c. of cells in a half-inch tube make the thickest layer in which it is possible to get a homogeneous growth of parasites.

"We have been able to secure growth of all the parasites in about twice this quantity of cells in a 1.25 cm. tube by employing tubes with a paper shelf suspended in them. They are filled with serum to at least 1.25 cm. above the level of the support for the paper disk. The disk is then carefully tucked in place, after which the cells are placed on it.

"We have obtained even more satisfactory results with tubes filled 1.25 cm. deep, or more, with freshly prepared human plasma. These are conveniently prepared by placing 1.25 to 2.5 cm. of blood, immediately after it is drawn, in culture tubes and centrifugalizing to throw the cells to the bottom before coagulation takes place. By continuing centrifugalization until after coagulation occurs, a flatter surface is secured for the plasma than if it is discontinued before this time. In such plasma bottom tubes 1.25 cm. of fresh dextrose serum is placed and then cells and parasites from the centrifugalized and defibrinated dextrose blood are carefully distributed over the surface of the plasma. We have sometimes obtained in these tubes a layer of live parasites approximately 0.25 cm. thick.

"Parasites in such leukocyte-free cultures develop, segment, and most of the merozoites enter new red blood-cells. These young parasites develop in the same manner as the first generation and sometimes reach the stage of segmentation. In fact, we have in one instance observed the development of three successive generations in such a culture. More often, however, the parasites begin to die out after the first segmentation and especially after the second. We have not been able to determine exactly the cause of this. In order to perpetuate the culture it is necessary to transfer a portion of the cells and parasites to a recently prepared tube containing fresh cells and serum. It is convenient to place the fresh serum in the culture tube and to take up in a large capillary pipet a portion of the cells and parasites of the culture and then about five times the amount of fresh cells. These are mixed in the pipet (avoid air) and then carefully spread on the surface of the plasma, paper shelf, or bottom of the tube, according to the particular kind of culture tube used. The transplantation should be done within four or five hours of the time of maximum segmentation and therefore approximately every forty-eight hours for tertian and estivo-autumnal parasites.

"It often occurs that with each successive transplant fewer parasites survive than in the previous one, and finally the culture is lost. In fact, there is little or no increase in the number of parasites in the body of man in most instances. Actually not more than one merozoite out of every fifteen to thirty survives. With the most exact technic we have secured a fifth generation containing many more parasites than the first,

and there is good reason to believe that with sufficiently exact manipulations it will be possible to continue the cultures indefinitely."

The only essential change which has been made in the requirements given above are that further experience has shown that the plasmodia grow as well at 37° C. as at higher temperatures, except that possibly they grow a little more rapidly at higher temperatures, and that it is not necessary to remove the leukocytes by centrifugalization, in order to grow more than one generation.

D. *The Distribution of Malaria Parasites Outside of the Body.*—There is only one place in the world in which malaria parasites live in nature outside of the body of man and that is in certain favorable species of mosquitoes.

E. *Modes of Conveyance.*—Many investigators have succeeded in transmitting malaria by taking the blood from an individual who has malaria and injecting it into another individual. Successful inoculations have been made both by the intravenous and the subcutaneous routes.

Hereditary transmission does not take place. There have been a few instances in which malaria has been reported in very young babies, but in few if any of them could the question of postnatal infection be ruled out. The majority of observers at the present time agree that prenatal infection does not take place. When we recall the structure and arrangement of the barriers that it would be necessary for the parasites to pass, it does not seem at all reasonable that infection could take place in this way.

(a) *Malaria Carriers as a Source of Infection.*—The term "malaria carrier" is usually applied to persons who have malaria parasites in their blood but who do not show active clinical symptoms. Of course a person with clinical symptoms is also a carrier of malaria and likely to be a source of infection. Persons who have latent malaria and who perhaps have never shown any recognized symptoms may also be sources of infection.

The importance of malaria carriers in the transmission of malaria and in its control has not been, as a rule, fully appreciated. It is surprising, in a locality where malaria prevails to any considerable extent, to note how many people who have not had recognized clinical symptoms of malaria will be found upon blood examination to have malaria parasites. In our Bolivar County experience, which is perhaps the most extensive investigation along this line that has ever been made, out of 18,782 persons who claimed not to have had attacks of malaria or evidences of attacks during the previous twelve months, 15.93 per cent. were found, upon the first examination made of their blood, to have malaria parasites. Out of the total 31,459 persons in an area of 325 square miles in Bolivar County whose blood was examined, 21.18 per cent. were found, upon first examination, to have malaria parasites. Not more than 10 per cent. of these were actually sick of malaria at the time. It is found, therefore, that in this locality, which is believed to be

representative of the malaria section of the Mississippi Delta, 21.18 per cent. of the entire population are potential malaria carriers. In fact, it is very certain that repeated examinations would have revealed considerably more infected persons and would have considerably raised the percentage of the population found to be malaria carriers.

Not all carriers have gametes in their blood at all times, and therefore not all are sources of infection to mosquitoes at any given time. They are, however, potential sources of infection and must be considered as such. If a man has one malaria parasite in his blood he may later have gametes in sufficient numbers to infect mosquitoes.

Improper treatment is largely responsible for the large number of carriers to be found in any malarious locality. Small doses of quinin not only do not disinfect the infected individual but they tend to increase the production of gametes. The use of chill tonics and drugs containing small quantities of quinin is very extensive in malarious regions. These seldom disinfect those who take them, but transform them from persons sick of malaria to unrecognized malaria carriers, and in all probability actually increase the amount of transmission of malaria which takes place.

The importance of disinfecting malaria carriers and thereby reducing transmission is the basis of one method of malaria control. There is a difference of opinion as to the probable value of this method, but in the author's judgment it is by far the most promising method at the present time. It is true that it should always be combined with such mosquito control as is practical, but up to the present time extensive malaria control by control of mosquitoes has not been accomplished except at a cost which would prohibit its application in extensive areas.

(b) *The Dissemination of Malaria by Mosquitoes.*—Malaria is carried from one individual to another by mosquitoes and in this way only. If there were no mosquitoes there would be no transmission of malaria. Not all species of mosquitoes are capable of serving as hosts for malaria parasites. All of the malaria transmitters so far identified belong to the sub-family Anophelinae. Deaderick and Thompson¹⁰ give the following list of Anophelinae which have been determined with more or less certainty to be malaria carriers:

Anopheles annulipes.
Anopheles bifurcatus.
Anopheles coxasa.
Anopheles crucians.
Anopheles farauti.
Anopheles formosensis.
Anopheles maculipennis.
Anopheles martini.
Anopheles pseudopunctipennis.
Anopheles pursati.
Anopheles quadrimaculatus.

Anopheles tarsimaculata.
Anopheles vincenti.
Cellia albimanus.
Cellia argyrotarsus.
Cellia pharoensis.
Cyclolepteron grabhamii.
Myzomyia christophersi.
Myzomyia culicifacies.
Myzomyia funesta.
Myzomyia hispaniola.
Myzomyia ludlowii.

<i>Myzomyia lutzi</i> .	<i>Nyssorhynchus annulipes</i> .
<i>Myzomyia picta</i> .	<i>Nyssorhynchus jamesii</i> .
<i>Myzomyia rosii</i> .	<i>Nyssorhynchus maculatus</i> .
<i>Myzomyia turkhudi</i> .	<i>Nyssorhynchus maculipalpis</i> .
<i>Myzorhynchus barbirostris</i> .	<i>Nyssorhynchus stephensii</i> .
<i>Myzorhynchus coustani</i> .	<i>Nyssorhynchus theobaldi</i> .
<i>Myzorhynchus fuliginosus</i> .	<i>Nyssorhynchus willmori</i> .
<i>Myzorhynchus paludis</i> .	<i>Pyretophorus chaudoyei</i> .
<i>Myzorhynchus sinensis</i> .	<i>Pyretophorus costalis</i> .
<i>Myzorhynchus umbrosus</i> .	<i>Pyretophorus jeyporensis</i> .
<i>Myzorhynchus ziemanni</i> .	<i>Pyretophorus superpictus</i> .

Of the mosquitoes that may serve as hosts for malaria parasites, not all are equally efficient. Not only is this true, but the habits of some of those that are easily infected under experimental conditions are such that they are not likely to be a considerable source of transmission. Some of the wilder species, although perhaps more easily infected, are not as likely to be a means of transmission as other species not so easily infected but more domestic and more likely to feed upon human beings.

(1) *Breeding-places*.—Different species of *Anopheles* have quite different breeding habits, but most of them require fairly clean water. They also require more or less protection by vegetation, such as grass, weeds, brush and trees. Deaderick and Thompson say:

“Ground water appearing at the surface is especially suitable. Pools of at least some degree of permanence are preferable to those which might dry before the aquatic stage of the insect is completed. Natural accumulations of water more often contain *Anopheles* larvæ than do artificial collections. Pools, ponds, swamps, inlets of lakes, and of small, slowly flowing streams, ditches along roadsides, canals, borrow pits along railroads and levees, and rice fields are common breeding-places. Water contained in the tracks of animals may harbor larvæ.

“When water is scarce, as during the dry season, anopheline larvæ may be found in tubs, barrels, buckets, bottles, cisterns, mollusc and coconut shells, in water retained by the leaves and stalks of tropic plants, or even within vases in dwellings, although these locations are to be regarded as places of necessity and not of choice.”

The eggs of *Anopheles* are deposited singly on the surface of the water or at the edge of some floating trash or debris. They vary in the length of time required to hatch, depending upon the temperature and perhaps upon other influences, but they may hatch in from two to four days under favorable conditions.

(2) *Identification of Anopheles Larvæ*.—It is not considered within the scope of this section to enter extensively into the description and identification of *Anopheles* in their different stages. It will be sufficient to say that *Anopheles* larvæ may be recognized for all practical purposes by their resting position in water. They remain parallel to the surface of the water, whereas the larvæ of all other species of mosquitoes rest at a considerable angle to the surface of the water. The

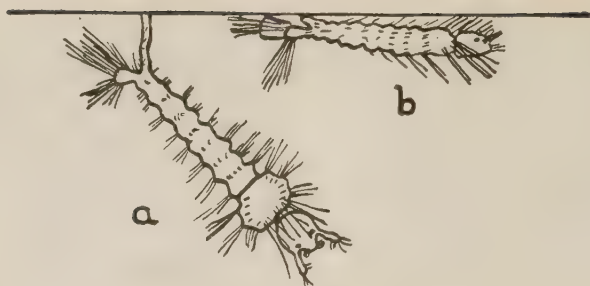


FIG. 8.—RESTING POSITIONS OF LARVÆ.
a, *Culex*; b, *Anopheles*.

larval stage lasts from twelve to fourteen days under favorable climatic conditions. In colder climates and during the cold season the larval stage may last many weeks. It has been demonstrated by Griffiths and others that *Anopheles* can pass the winter in the larval stage.¹¹ This, no doubt, is an important source of the first mosquitoes following the cold season. Whether many adults pass the winter is open to question. It is quite certain that a very small proportion of those alive at the beginning of the winter survive.

The duration of the pupal stage may be from about two to four days under favorable conditions. The pupæ are also quite resistant to cold. From the pupa the full-grown imago emerges and after remaining for a very short time flies away.

(3) *Identification of Adult Anopheles*.—For all practical purposes *Anopheles* may be differentiated from all other species of mosquitoes by their position when resting on a wall. The proboscis, head, thorax and abdomen are in the same line and form quite an angle with the surface upon which the insect rests. In some species almost a right angle is formed. This is in contrast to all other species. The chief malaria carriers of the United States are *Anopheles quadrimaculatus*, *Anopheles maculipennis* and *Anopheles crucians*. King¹² has shown that *Anopheles punctipennis* is also a host of malaria parasites.

(4) *Flight Habits of Anopheles*.—LePrince has probably made the most extensive investigations of the flight habits of the malaria-bearing mosquitoes. Experiments were conducted in Panama¹³ in which *Anopheles* were marked by spraying them with a solution of eosin and then liberating them. Collections were made during the following several days and the mosquitoes collected were examined for the presence of the dye. Forty stained specimens were recovered at a distance varying from 1200 to 6250 feet from the liberation station. Five specimens were captured at the greater distance.

LePrince and Griffiths¹⁴ made numerous investigations of the flight habits of *Anopheles quadrimaculatus* in South Carolina, employing the same method of identification that was followed in the Panama studies. These observations show that under certain conditions at least, *Anopheles*

quadrinaculatus will fly as far as one mile from the point of liberation. In one observation where the production at the breeding-place was considerably less, the greatest distance over which flight was found to have taken place was approximately half a mile. In one test the marked specimens flew a distance of 3090 feet, 800 feet of which was over a river, in returning to the cabin in which they were first captured.

It is noteworthy that out of 270 *Anopheles quadrinaculatus* that were liberated at a distance of 3090 feet from the place where they were captured, two of them were recaptured in the same cabin within seventy-two hours after their liberation. This not only has significance as to the distance over which mosquitoes fly, but also emphasizes the idea of their tendency to return to the house from which they came. The author considers this an extremely important feature of malaria transmission that has perhaps been somewhat overlooked. Not only do mosquitoes tend to return to the same breeding-ground where they were bred, after securing a blood-meal, but there is also a tendency for them to return to the same feeding-ground after ova-position. For this reason, especially in rural communities, a malaria carrier in a given house is much more likely to be a source of infection to persons living in the same house than he is to others living in the community.

The distance over which *Anopheles* may fly under exceptional circumstances is not as important as the distance over which they actually fly under ordinary conditions in sufficient numbers to be likely to transmit malaria. Generally they do not fly over clear ground for as long distances as they do over ground where they are protected more or less by a growth of trees or rank vegetation. Being swamp or jungle species most of them do not venture great distances away from such protection from their natural enemies as is afforded by a dense growth of vegetation. *Anopheles* will follow a hedge row or a lead of trees for much longer distances than they will fly over clear ground. In the rural farming section, crops, such as corn and cotton, frequently offer favorable protection and leads for mosquitoes to reach residences situated so far from their breeding-ground that they would not reach them otherwise.

(5) *Length of Life of Mosquitoes*.—No doubt the longevity of different species of mosquitoes varies greatly and there is also no doubt that there is a great variation in the length of time mosquitoes of the same species live under variable conditions. Many species are known to pass the winter in either a hibernating or an inactive condition. The manner in which the active processes are minimized and the length of life greatly prolonged by special influences is indicated by an observation of Mitzmain¹⁵ in which it was found that gravid females did not deposit eggs as long as they were kept at temperatures of from 4.5° to 12.5° C. In another experiment some eggs were laid at temperatures ranging between 13.5° C. and 16.5° C. At warmer temperatures the life processes are much more active and no doubt the life of the insect is much shorter. When mosquitoes are kept under artificial conditions in the laboratory, the mortality is very high. A large part of them live only a few days. One cannot conclude, however, from this that the duration of life of

Anopheles in nature is so short. It is a fact, however, that whenever mosquito-breeding is stopped in a locality where the insects are abundant, it takes only a week or two for a marked reduction to be noticeable. The average length of life of *Anopheles* must therefore vary greatly from about two or three weeks under some conditions up to at least three or four months under winter conditions. It must be understood, however, that of the large number alive at the beginning of the winter, only a very small proportion survive to the next warm season.

F. *Types of Infection*.—In simple tertian infection there may be one crop of parasites segmenting on one day and another crop segmenting on the alternate day, giving rise to quotidian fever. This is properly called double tertian infection. The most frequent type of infection, however, is single tertian in which there is only one crop of parasites, giving rise to tertian fever.

In quartan malaria there may be one, two or three crops of parasites, giving rise to quartan fever, or to quotidian on two days followed by an intermission of one day, or there may be three crops of parasites, giving rise to quotidian fever. The tendency to reproduce by crops is not so marked in the estivo-autumnal type; in heavy infection, especially, there are sufficient parasites reproducing at all times to give rise to continued fever without intermission.

In addition to these various types of pure infection, there may be mixed infections of two or three different species. It happens very frequently in localities where two species of malaria parasites are prevalent that an individual may be infected with both. It often occurs that an individual may have tertian infection during the spring and early summer and estivo-autumnal in the fall and winter. It is not common, but occasionally happens that gametes of both may be found simultaneously in the blood of an individual. One may sometimes find a few crescents in the blood of cases where all the schizonts found are tertian. Usually in cases of mixed infection one parasitic form predominates and determines the clinical picture.

Symptomatology.—CLINICAL HISTORY.—*Period of Incubation: Symptoms of Incubation Period.*—The period of incubation is necessarily influenced very greatly by the number of sporozoites introduced. For instance, the length of time required for sufficient multiplication to give rise to clinical symptoms would be very much longer where the individual had been bitten by only one infected mosquito than in another instance in which he had been bitten by many, each one introducing a number of sporozoites. It is conceivable that clinical symptoms might possibly develop after forty-eight or seventy-two hours, according to the species of malaria parasite, provided an enormous number of infected mosquitoes fed upon the individual. Barber¹⁶ reported two cases in which the first rise of temperature occurred from fourteen to seventeen days after experimental inoculation by infected mosquitoes. These were *Anopheles rossi* infected with estivo-autumnal parasites. Mitzmain,¹⁷ experimenting with *Anopheles punctipennis* infected with tertian parasites, allowed from one to four mosquitoes to bite each of seventeen dif-

ferent persons. The incubation period in the fourteen who developed malaria is shown in his table, reproduced below (Table 4).

TABLE 4.—LENGTH OF TIME EACH PERSON WAS BITTEN AND INCUBATION PERIOD RESULTING. (Miltzmain)

Date When Bitten	Volunteer	Infected <i>Anopheles punctipennis</i> Applied				Incuba- tion Period (Days)
		No. 18	No. 23	No. 24	No. 25	
1916						
Feb. 17	H. E. H.	1 minute	45 seconds	45 seconds	40 seconds	15
" 18	Dr. H. A. T.	Complete	Complete	14
" 21	Dr. R. C. D.	40 seconds	1 minute	13
" 21	Dr. T. H. D. G.	30 seconds	40 seconds	14
" 21	F. M. H.	1 minute	45 seconds	14
" 21	R. E. T.	30 seconds	80 seconds	15
" 22	Dr. R. T. O'N	1 minute	15
" 23	H. T.	40 seconds	1 minute	13
" 23	Dr. S. L. C.	40 seconds	30 seconds	13
" 26	F. W.	50 seconds	16
" 26	F. A.	1 minute	1 minute	14
" 28	C. B.	Complete	Complete	13
Mar. 1	T. A. R.	35 seconds	19
" 1	G. O.	1 minute	18
" 2	J. M.	50 seconds	Neg.
" 2	J. W.	1 minute	Neg.
" 3	W. P.	20 seconds	Neg.

On the basis of blood inoculations, Marchiafava and Bignami¹⁸ estimated the incubation period to be from eleven to eighteen days.

Mannaberg⁴ describes an observation made by Sorel in which eighteen men developed malaria in from seven to nine days after their first exposure to natural infection. It seems that they were exposed to very heavy infection, which would furnish an explanation for the fact that the incubation period was somewhat shorter than that observed by others. With reference to the duration of the incubation in experimentally produced malaria, Mannaberg⁴ says: "Quartan fever shows, in five cases, incubation periods of from 11 to 18 days; the average, therefore, is 13.4 days. Tertian fever shows, in seven cases, incubation periods of from 6 to 21 days; the average is, therefore, 11 days. Seven cases with parasites of the second group (ameboid, with and without crescents) show fluctuations between 3 and 14 days; the average is, therefore, 6.5 days. In two cases showing crescents without (probably with small numbers of) ameboid parasites, the incubation period was 13 to 15 days, the average being, therefore, 14."

The data available leads the author to set the limits for the vast majority of all cases of natural infection at from 6 to 21 days. It is quite possible that in rare instances it may last much longer than that, and in fact persons may become infected and carry their infection for months

without ever showing recognized clinical evidence. It is possible that individuals who have so much resistance as to make this possible may finally eliminate the infection without ever having shown any clinical signs. It would even be possible for such an infection to exist and yet no parasites be found upon blood examination, because of the small number present at the time of examination. This view is especially supported by the observation that in localities where malaria is very prevalent blood examinations frequently prove considerable numbers of persons to have parasites in their blood who are not sick at the time and who have not had any evidence of malaria, so far as they know. Many of these carriers of light infection finally lose their infection without ever having clinical evidence of its presence and without undergoing any treatment whatever.

Usually there are no recognized symptoms during the incubation period. It does happen, however, that the patient may have one paroxysm of chills and fever, and sometimes two, before any malaria parasites are found in the peripheral blood. Frequently the first paroxysm is considerably milder than those following it. Although it is not possible to make a certain diagnosis of malaria until malaria parasites are demonstrated, there is no doubt that the one or two paroxysms which sometimes occur before parasites are demonstrated are a part of the disease and can therefore hardly be included in the incubation period. In those cases which do not develop clinical symptoms early, or at all, there are of course no recognized symptoms of the incubation period. There is no doubt that the infection has a definite systemic effect. It may, however, be so slight that it is not recognized by the individual, nor could it be recognized in many instances by a most careful medical examination.

Mode of Onset and Symptoms during Progress of Disease.—The great variation in the symptoms of malaria can best be appreciated if we look upon it as an infection by parasites and not as a disease. It is simply a case of the presence of parasites in the blood and especially in certain organs and tissues of the body. The reproduction of these parasites is controlled to a large extent by the resistance of the individual. The resistance may, in some instances, be sufficient to destroy all the parasites and to prevent the production of sufficient numbers to give rise to any clinical symptoms. On the other hand, the resistance may be very poor, so that the parasites are able to reproduce at a rapid rate. A certain amount of restraint, however, is probably always present. Some infected individuals never develop clinical symptoms, as has already been stated. Whenever attacks develop, however, the onset is usually rather sudden. The patient may experience a certain amount of malaise, headache, etc., for an hour or two before the onset of the chill.

The chill is the most frequent symptom of the onset of an attack of malaria, although it is sometimes absent. It is less likely to occur in young children than in older persons. The chills of malaria almost always occur during the day, but the first one may sometimes occur at

night. Such a night attack generally comes before 8 or 9 P.M. and after 4 A.M. The first chill is usually lighter than those which occur later, but sometimes it is quite severe. The duration of the chill is also extremely variable but usually lasts from a few minutes to half an hour or sometimes a little longer.

Severe headache and general aching, especially in the back and limbs, set in during the chill if they are not already present. These symptoms increase with the fever until the maximum temperature is reached. When the fever "sweats off," as it generally does, the aching usually goes with it.

Nausea and vomiting are common symptoms of the onset of a malarial paroxysm and often continue during the height of the fever.

Convulsions not infrequently occur at the onset and during a malarial paroxysm in children, especially when it is accompanied by very high fever.

The temperature begins to rise at the time the chill sets in, or sometimes from a few minutes to an hour earlier. During the chill the rectal temperature usually shows an elevation of two or three degrees. The temperature reaches its maximum within an hour or two after the onset of the chill and lasts from an hour or two to several hours in different individuals. Malaria is a disease characterized by high temperature, although in many instances it does not rise very high. Temperatures of 104° and 105° F. (40° and 40.6° C.) are the common maximum in ordinary intermittent malaria. Temperatures of 106° or 107° F. (41.1° or 41.7° C.) have been observed, although, of course, they last for only a short period of time. The fever usually lasts from two or three to six, eight or ten hours and then begins to subside rapidly with the onset of the sweating stage.

A decline in the elevation of temperature marks the beginning of the sweating stage. The patient becomes quiet and usually goes to sleep. Profuse perspiration usually lasts for an hour or more, and finally the temperature reaches approximately normal. The patient soon feels fairly well except that he is somewhat weakened and "used up" from the paroxysm. In most cases the patient continues to feel better until the onset of another paroxysm.

In simple tertian malaria the paroxysm characterized by chill and high fever lasts for from one to several hours. The symptoms rapidly subside, usually giving way to profuse perspiration. It seldom occurs that the temperature does not return to the normal before or during the night following the attack. The patient feels fairly well, except for the weakness and depression due to the paroxysm, until about forty-eight hours after the onset of the first paroxysm. Another attack of chills and fever occurs, usually beginning at almost exactly the same time of day and running about the same course, except that in persons whose resistance is not strong there is a tendency for the paroxysms to be more severe. In persons who are controlling the infection, or eliminating it, the onset of the paroxysms tends to occur later each time. On the other hand, in those who are not putting up a good fight,

the tendency is for each subsequent paroxysm to set in earlier than the preceding one. In simple tertian malaria where only one crop of parasites is present, giving rise to tertian chills and fever, these attacks occur with great regularity every other day indefinitely, if not influenced by treatment, by the resistance of the patient or by some other factor. In the instance of two crops of malaria parasites segmenting on alternate

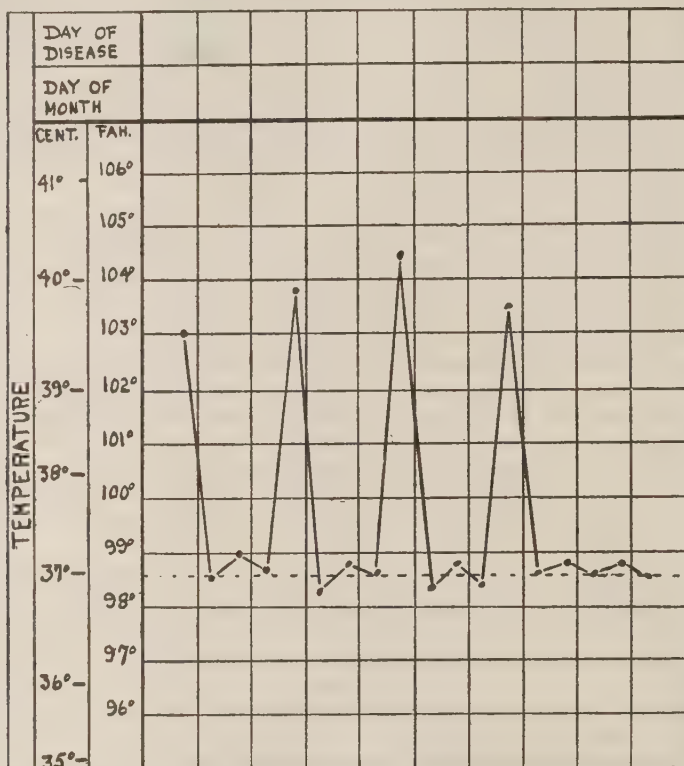


FIG. 9.—TEMPERATURE CHART OF SINGLE TERTIAN INFECTION.

days, chills and fever occur every day instead of every other day. The tendency is, however, for the paroxysm produced by each crop to occur at the same time of day as that produced by the other.

In quartan malaria the onset is almost exactly like that of tertian but usually less severe. The paroxysms, both chills and fever, are also generally less severe. The duration of a paroxysm is about the same as in tertian. If only one crop of parasites is present, the paroxysm recurs at seventy-two hour periods and not at forty-eight hour periods as in tertian. It sometimes happens that there are two crops of parasites, one segmenting on one day and one on the next and none on the next,

giving rise, of course, to paroxysms on those days. Sometimes, also, there may be a crop of parasites segmenting on each day, giving rise to a daily paroxysm. This occurs at the same time each day, or at least tends to do so.

The mode of onset of estivo-autumnal fever is frequently very similar to that of tertian or quartan, and there may be some prodromal symp-

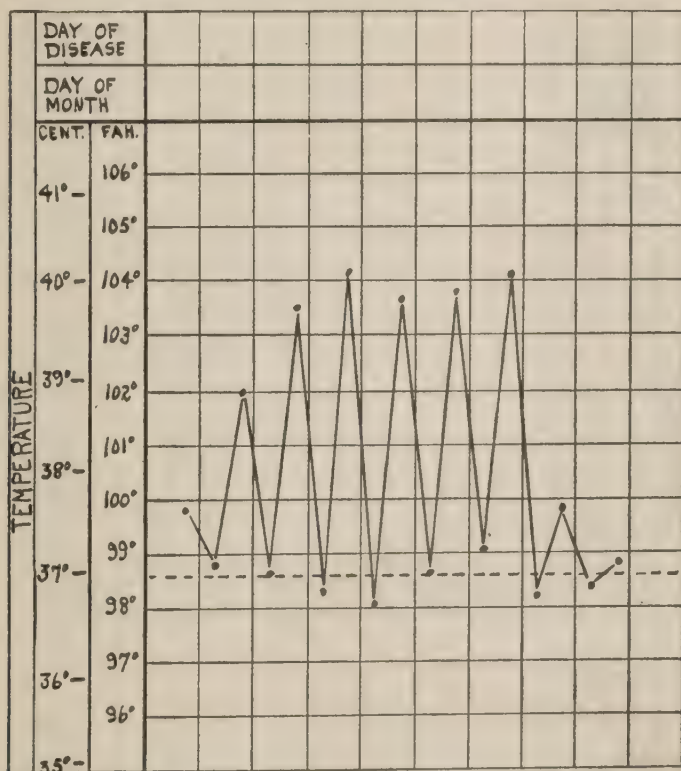


FIG. 10.—TEMPERATURE CHART OF DOUBLE TERTIAN INFECTION.

toms; but usually the rather sudden development of a chill followed by fever is the first thing noticed. Accompanying the chills and fever are also the characteristic headache and aching in the back and limbs. Estivo-autumnal infection may give rise to intermittent chills and fever whenever the parasites segment chiefly by crops, as they generally do, or it may give rise to continued fever after the first chill occurs. In some instances we have regular every-other-day chills and fever or tertian malaria. More frequently there are two crops of parasites segmenting on alternate days, giving rise to chills and fever every day. There is a tendency for the fever to last longer following the chill; also there

is less tendency for every paroxysm to be ushered in by chills. In the case of two crops of parasites, it frequently happens that there is more or less continuous segmentation, giving rise to continued fever, the temperature remitting, but not reaching the normal during the twenty-four hours. Usually no chills occur after the first one or two in such cases. There is no remarkable difference between the chills and fever of

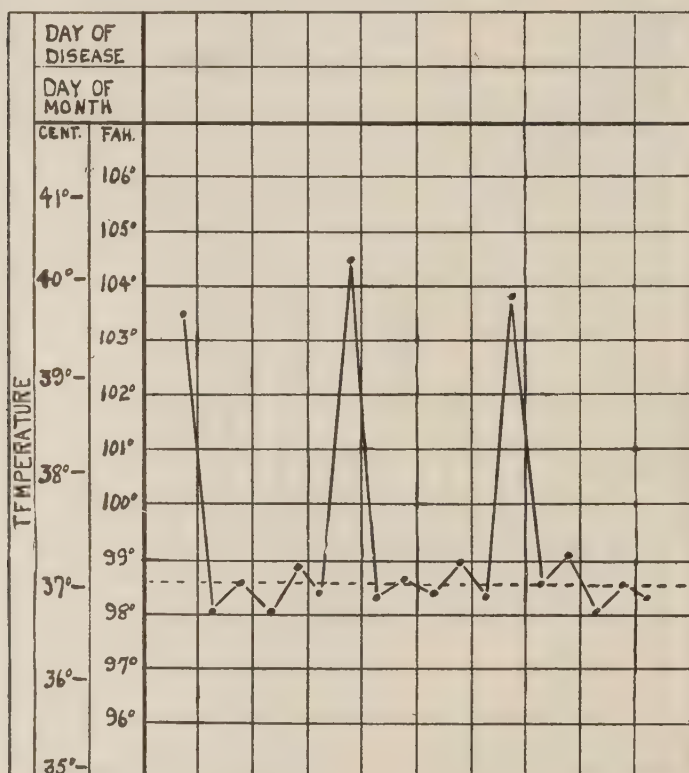


FIG. 11.—TEMPERATURE CHART OF SINGLE QUARTAN INFECTION.

tertian, quartan and estivo-autumnal malaria. The noteworthy difference in the three forms is that tertian and quartan are almost always intermittent, whereas estivo-autumnal may be intermittent but is frequently remittent.

In those clinical types in which the symptoms are very severe, malaria is frequently spoken of as pernicious. Nearly all cases of pernicious malaria are produced by the estivo-autumnal parasite, although occasionally the tertian or quartan parasite may produce pernicious symptoms or actually death. The so-called quotidian estivo-autumnal parasite is usually the one responsible in pernicious malaria. Some-

times the chill is especially severe and prolonged. It may or may not be accompanied by very high fever, severe gastro-intestinal symptoms or convulsions. In the event of death or threatened death due to such a case of pernicious malaria, the chill would be called a "congestive chill." The blood in such cases shows larger numbers of parasites than are usually present in the more benign clinical types. Usually the greater

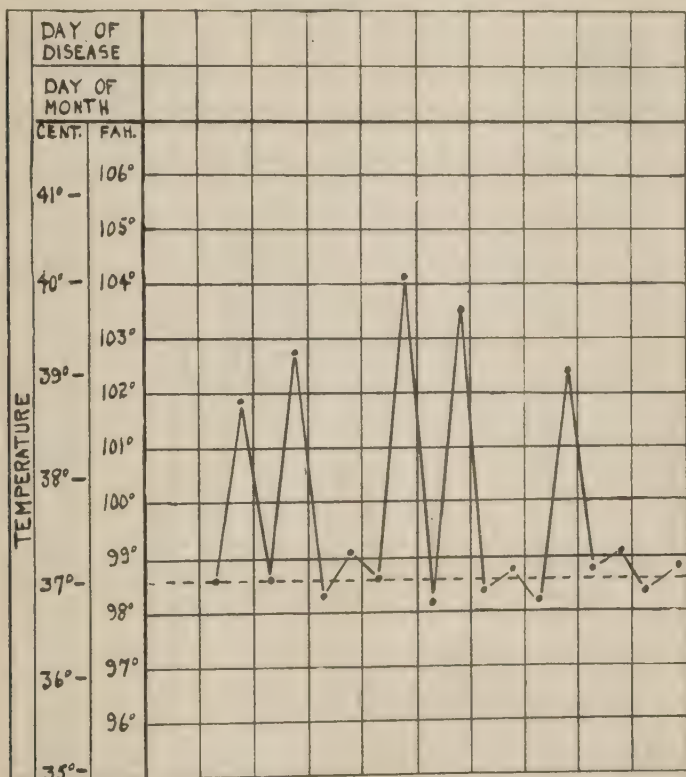


FIG. 12.—TEMPERATURE CHART OF DOUBLE QUARTAN INFECTION.

number of the parasites offers sufficient explanation for the greater severity.

Sometimes, for reasons not at present well understood, "hematuria" or, more correctly speaking, hemoglobinuria, develops. Just what occurs to produce this condition is not known. In hemoglobinuria, usually following a chill, the urine is noticed to be of a deep claret or almost coffee-black color. Great depression is usually present. Within from twenty-four to forty-eight hours jaundice begins to appear and, except in the mildest cases, develops rapidly, until the skin and sclera are a pronounced saffron yellow. In favorable cases, the hemoglobin in the

urine may clear up almost as rapidly as it set in. In less favorable cases it may continue to increase, especially following the next chill. The chills of hemoglobinuria do not occur with the same regularity as they do in other forms of malaria. However, there is a marked tendency to periodicity, and in many instances they do occur almost as regularly as they do in ordinary malaria, chills and fever.

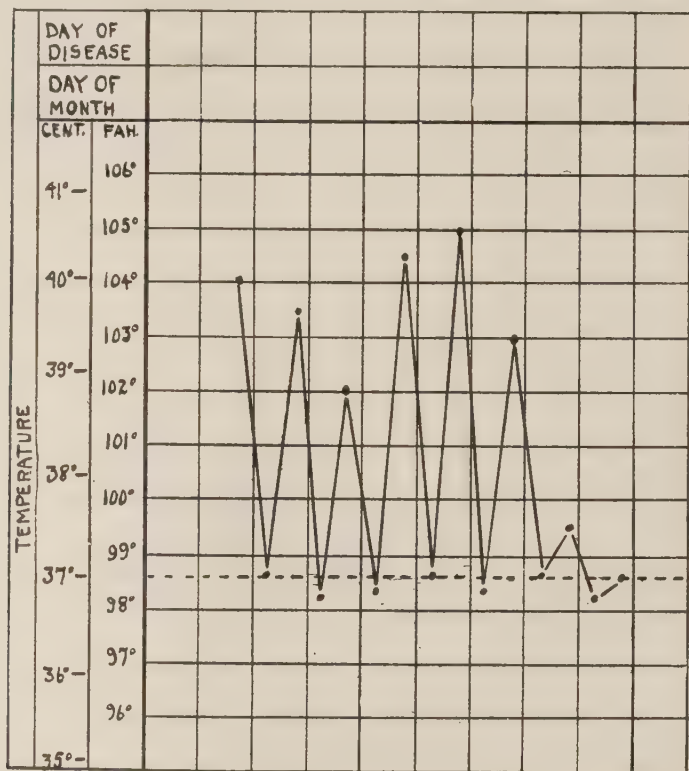


FIG. 13.—TEMPERATURE CHART OF TRIPLE QUARTAN INFECTION.

There is no uniformity in the elevation of temperature occurring in hemoglobinuria but, generally speaking, the fever is not high, ranging from 101° to 105° F. (38.3° to 40.6° C.). When the disease is progressing, it is usually remittent in type, but occasionally intermittent.

The quantity of urine decreases, accompanied by the production of casts. In cases that progress to a fatal termination, anuria almost always occurs, often several hours and sometimes several days before death. The anuria is said to be due to the plugging of the renal tubules and to diminution of blood-pressure. It occasionally happens that urinary secretion is reestablished after more or less complete suppres-

sion for several days; in such cases recovery takes place. The depression and low blood-pressure are striking features of the disease. The blood-pressure is frequently approximately 70 or 80 mm. of mercury.

Another important form of pernicious malaria is the cerebral or comatose type. The onset is sudden, but usually it occurs in persons who have had several previous paroxysms or who have had active clinical

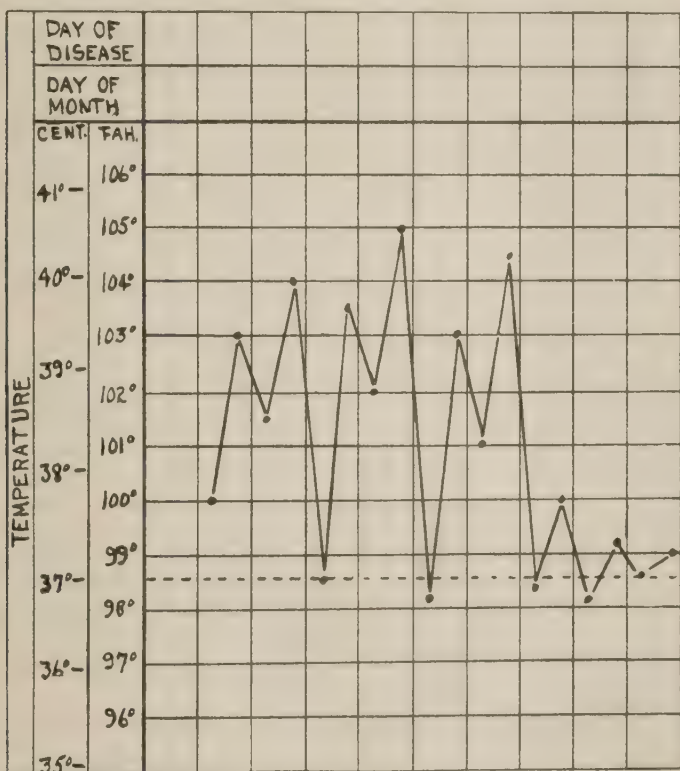


FIG. 14.—TEMPERATURE CHART OF TERTIAN ESTIVO-AUTUMNAL MALARIA.

symptoms of malaria for at least several days. It is practically always caused by estivo-autumnal parasites and varies very greatly, depending upon the number of parasites obstructing the capillaries of the brain, and upon the extent and location of the obstruction. No doubt some parasites lodge in the brain in all cases of malaria, but whenever they are sufficiently numerous, sufficient anemia of the brain is produced to cause coma. The profoundness of the coma varies very greatly, of course, as does also its duration. Sometimes it lasts only a few hours and passes away with the subsidence of the high fever. In other instances it continues and increases until the death of the patient, in spite

of any treatment given. Usually there are very large numbers of parasites present in the blood in these cases. In such instances delirium and unconsciousness are present, especially during the high fever period. They generally subside with the fever.

PHYSICAL FINDINGS.—It must be understood that malaria consists of an infection with one or more of three different species of malaria

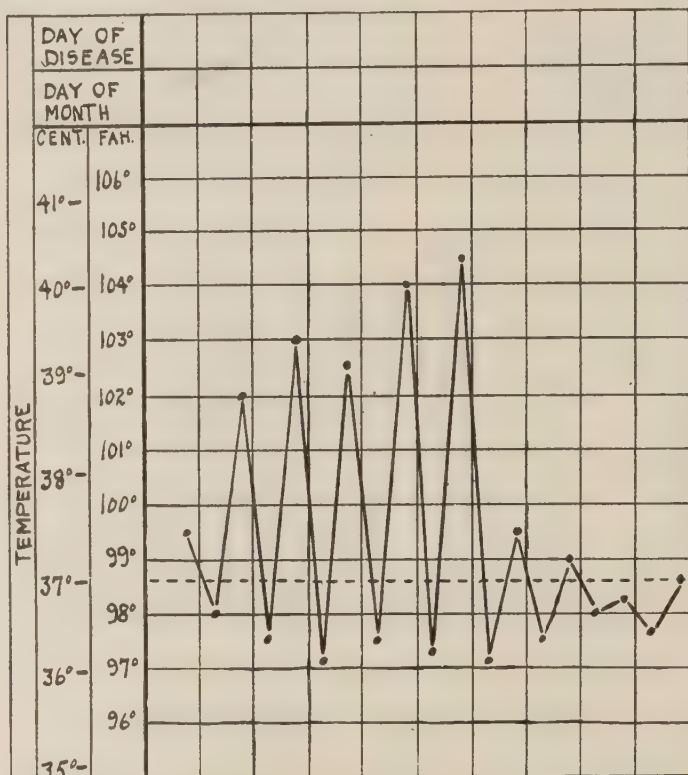


FIG. 15.—TEMPERATURE CHART OF QUOTIDIAN ESTIVO-AUTUMNAL MALARIA.

parasites, each of which produces somewhat different symptoms and may have a somewhat different effect, recognizable on physical examination. It must also be understood that the number of these parasites in different individuals may vary very greatly, from a number entirely too small to produce any recognized effect up to one sufficient to produce death. Between these two extremes there will be wide variations in the symptoms and findings upon examination. For instance, in the case of individuals who have been infected with malaria parasites but have sufficient resistance to prevent their multiplying to any considerable extent, it may be that nothing abnormal can be recognized by a physical

examination. There are, however, changes demonstrable by physical examination in practically all infected persons who have clinical symptoms due to malaria.

Observation.—During the first few days of a first attack of active malaria nothing abnormal may be recognized by observation. After a few paroxysms have occurred, however, there has usually been sufficient destruction of blood-cells so that a certain amount of anemia is present. As the disease continues, the anemia increases more or less, and sooner or later it will be noticed from the general appearance of the individual, as well as upon examination of the mucous membranes. Repeated paroxysms, or chronic malaria, result in a sufficient collection of the malaria pigment in the capillaries of the skin to give rise to a more or less muddy, cachectic appearance. This cachexia may be very marked in those who have had repeated attacks for long periods of time, especially when the attacks are due to estivo-autumnal parasites. The other parasites do not give rise to cachexia to anything like the same extent as the estivo-autumnal type. In fact, almost all cases of malarial cachexia are due to estivo-autumnal infection.

In the hemoglobinuric form, if it is at all severe, hematogenous and perhaps hepatogenous discoloration of the skin appears soon after the appearance of the hemoglobinuria. In severe cases this is frequently very marked and the appearance of the patient is quite similar to that of one suffering with yellow fever. In addition to this hematogenous change which is found more or less in cases of hemoglobinuria, there is sometimes sufficient hepatitis in other forms of malaria, where for some reason or other the parasites especially localize in the liver, to give rise to considerable bile-staining of tissues and to a jaundiced appearance.

In the pernicious, comatose cases the patient is observed to be in a more or less profound state of coma. Usually the pupils are dilated.

Palpation.—One of the positive changes revealed by palpation in malaria is the enlargement of the liver which occurs in a large proportion of all cases that have continued for any considerable length of time. In chronic, cachectic cases, especially in those of long standing, the border of the liver is usually readily palpated well below the costal border. It is firm and hard but not so strikingly so as the accompanying enlarged spleen.

The other change to be recognized by palpation is in the spleen which is enlarged and hard in most cases of malaria where clinical symptoms have continued for more than a few days. The spleen is enlarged in all cases of clinical malaria and in all forms of the disease, but the enlargement is greater in the tertian and estivo-autumnal form than in the quartan. During the first few days of a first attack of malaria it may be impossible to palpate the spleen, but after that the border can usually be felt extending more or less below the costal border, depending upon the duration and severity of the attack and perhaps also upon the individual case and the type of infection. In chronic cases of long standing it is not uncommon for it to extend below and to

the right of the umbilicus. These very large spleens are usually extremely hard. In most instances they can be felt without difficulty, and if the abdomen is at all relaxed one can usually grasp the organ in the hand and palpate it with great ease. In such cases, the patient himself frequently feels and recognizes the enlarged spleen.

The spleen can be palpated best with the patient in the recumbent position and with the knees drawn up to relax the abdomen. The *technic* is as follows: Stand on the right side of the patient and place the left hand over and beyond the region of the spleen so as to be able to lift it forward against the costal border and abdominal wall. Now with the right hand placed flat upon the abdominal wall, do the palpating with the tips of the fingers. Instruct the patient meanwhile to take a full inspiration and then to exhale. Repeat this two or three times in order to accustom the abdominal muscles to the hand on the abdomen and to obtain thorough relaxation. As the patient takes a full breath after having exhaled, lift the spleen forward with the left hand and gently press the tips of the fingers of the right hand against it. About the middle of the inspiration and after the spleen has been forced against the finger tips, which are pushed forward to meet it, raise the fingers somewhat and allow the spleen to slip beneath the finger tips. The sensation produced is striking and enables one to recognize the spleen without difficulty.

The frequency of enlargement of the spleen is so great in some countries that it is calculated as a means of determining the prevalence of malaria in the region. The author's observation has been that the spleen rate would be of little value in determining the endemic index in this country. It must be granted that it may be useful in other countries where malaria is much more prevalent than it is here, but it does not seem advisable to substitute it for the more dependable blood examination for this purpose.

Percussion.—Percussion does not reveal anything in malaria, but it may be an aid in outlining the size and location of the liver and spleen. Usually palpation is much more dependable, particularly for the purpose of recognizing enlargement of the spleen. Percussion is especially useful in determining the border-line of liver dullness.

Auscultation.—There is nothing abnormal to be found by auscultation in malaria except perhaps in the extremely rare, so-called pneumonic form, in which there are large numbers of parasites lodged in the capillaries of the lungs. Râles and other evidences of hyperemia may be found, but it is always doubtful whether they are due entirely to the malaria or to secondary or accompanying conditions. There is no reason why there should not be cases of malaria and pneumonia occurring simultaneously in the same individual. In fact, such is the case, and the author doubts whether there is such a form of malaria as the pneumonic form, due to malaria only.

Special Tests—Reflexes, etc.—In comatose and other pernicious forms of malaria the reflexes may be diminished and there may be paresthesia. These are to be found especially in extreme cases. If we

understand that a large proportion of such cases, if not all of them, are caused by the collection of large numbers of parasites in the capillaries of the brain and perhaps of the cord, and by the localization of the parasites in different parts of these particular organs, we will be prepared to expect various nerve phenomena in different cases. Delirium, tetany, tetanic or convulsive paroxysms upon irritation may occur in rare instances.

LABORATORY FINDINGS.—1. *Blood.*—Laboratory examinations of blood in malaria show many changes, varying with the intensity and duration of the infection. In many instances the resisting influences of the body are strong enough to prevent sufficient reproduction of malaria parasites to give rise to demonstrable effects upon the blood. On the other hand, in cases where there is very active multiplication of the parasites and consequent destruction of the red blood-cells, more or less anemia is produced. In the severer cases anemia is present to a very large degree. It is not uncommon to find hemoglobin readings as low as 50 or 60 per cent., and in some instances even as low as 40 per cent. This low reading is sometimes reached in a comparatively short time in the worst cases. Not only is there reduction in the hemoglobin reading, but there is also more or less reduction in the total count. Usually the count does not decrease as rapidly as the hemoglobin percentage does, and therefore we always have a color index below normal in uncomplicated malaria. In the severer cases, polychromatophilia, stippled and occasionally nucleated cells are found. Bad chronic malaria cases show almost as much granular degeneration of the red cells as any other condition except lead-poisoning, pernicious anemia and some of the leukemias.

The only change in the leukocyte count is an increase in the percentage of the large mononuclear cells. In most cases of malaria in which there are active clinical symptoms the count runs from about 6 per cent. to 15 per cent. or 18 per cent., sometimes even higher. It is not uncommon to find malaria pigment in the large mononuclear or endothelial leukocytes. Whenever the pigment is found, it is quite characteristic and diagnostic.

Malaria parasites are found in the blood in practically all clinical cases of malaria which have not been recently treated by quinin. Quinin causes the rapid disappearance of parasites, especially of the schizonts, and therefore in interpreting the presence or absence of parasites in a given case, one should always take into consideration information as to whether or not quinin has recently been taken. Even five or ten grains of quinin are frequently sufficient to cause the disappearance of parasites. The latter sometimes disappear as a result of quinin a short time before the disappearance of the clinical symptoms. In malaria patients who take sufficient quinin to cause the parasites to disappear from the peripheral circulation, the fever, or chills and fever, do not continue for any length of time after the ingestion of the drug.

(a) *Technic of Blood Examination for Malaria Plasmodia.*—There are three methods of examining the blood for malaria plasmodia, each

one of which has its advantages and application: (1) the ordinary "thin film method"; (2) the "thick film method," and (3) the "centrifuge method." The thin film method may be learned quickly and is by far the most practical for all ordinary purposes. The thick film method requires much more experience on the part of the operator, and in the hands of those with little experience, it is less reliable. In the hands of experienced workers, however, it results in great saving of time. From about three to ten times as much blood can be examined in a given length of time by this method as by the thin film method. Only those with special facilities and training are able to use the centrifuge method with success. When properly carried out it frequently results in the finding of parasites in blood when they could not be found by any other method. However, it is not to be recommended for general use.

Thin Film Method.—Prick the finger or ear lobe (a straight, Hagedorn needle makes a good blood stickler) and squeeze out approximately $\frac{1}{4}$ drop of blood. Touch this with the surface of a clean microscope slide at about the junction of the middle and outer third of the slide. Place the end of another slide in the drop and spread it out thinly. Most of the spread should be on the middle third of the slide. It should vary in thickness from too thick to see through on one end to as thin as possible on the other end of the spread. The blood spread dries quickly and should then be labeled by writing the name or initials of the patient across the face of it either with an ordinary lead pencil or, preferably, with a metal point (such as the blunt end of a needle). Such preparations may be kept for hours, days or weeks before they are stained and examined. However, better results are obtained if they are stained within from twelve to twenty-four hours after the time they are made.

There are many different stains that are quite satisfactory, various modifications of the Romanowsky stain being the best. Wright's stain is almost perfect for this purpose. The technic of staining is as follows:

- (1) Cover the preparation with the stain for one minute.
- (2) Dilute the stain on the slide with from one to four or five times as much water, preferably distilled, and allow to remain from three to five minutes.
- (3) Wash off, dry and examine with the oil immersion lens.

Thick Film Method.—For the thick film method blood is obtained in the same way, but a somewhat larger quantity is drawn. From one-half to one drop is preferred. Instead of being spread out thinly on the slide, the blood is made into a thick film by spreading it out somewhat with the corner of another slide. Usually half a drop of blood will make a spread of proper thickness, about half an inch in diameter. It should be as thick as can be decolorized and stained properly and examined satisfactorily. Experience will be the best guide as to the proper thickness.

Several different methods of decolorizing and staining these thick

film preparations have been recommended. A perfectly satisfactory one is as follows:

(1) Decolorize and fix the preparation in methyl alcohol (Merck's highest purity), containing 2 per cent. glacial acetic acid and 2 per cent. hydrochloric acid. It takes from one to three minutes to decolorize recently made preparations. Very old preparations are much more difficult to decolorize.

(2) Wash, preferably in running water, to entirely remove the acid. This requires only a minute or two.

(3) Stain in the polychrome methylene blue solution described below, for two or three minutes.

(4) Transfer without washing and stain in 1 to 1000 solution of eosin in water, for one-half minute.

(5) Transfer without washing and stain again in the polychrome methylene blue solution for one-half minute.

(6) Transfer without washing and dip once only into the eosin solution, after which wash immediately in running water. Allow the preparation to dry and examine with the oil immersion lens. Malaria parasites stain well, but have not exactly the same appearance as they have in the thin film because of the fact that they are not spread out, or rather that the red blood-cells containing them are not spread out flat on the slide. The platelets are stained more or less and there is also considerable foreign material and débris which may mislead one not familiar with malaria parasites in such a preparation.

Stock polychrome methylene blue solution is made by heating a 1 per cent. solution of methylene blue in water containing $1\frac{1}{2}$ per cent. of sodium bicarbonate, in a steam sterilizer for one hour. This is filtered and is known as stock solution of polychrome methylene blue. The staining solution is made by adding 2 c.c. of this stock solution to 100 c.c. of water. The dilute solution may be used for several days before making up a new staining solution.

The Centrifuge Method.—This method depends upon the fact that when defibrinated or citrated blood containing malaria parasites is centrifugalized under proper conditions, all the large parasites rise to the surface of the cell-column in the bottom of the tube.

Blood is drawn from the vein by means of a clean, dry syringe (or of a hollow needle only) and defibrinated by stirring it with a suitable glass rod or other instrument. Another equally satisfactory method of preventing coagulation is the addition of 2 c.c. of a 50 per cent. solution of sodium citrate to 10 c.c. of blood immediately after it is drawn.

Place the defibrinated or citrated blood in large centrifuge tubes so that the depth of blood is from 2 to 5 cm. Centrifugalize at about twenty-five hundred revolutions per minute for from one to three minutes. Most of the large parasites come to the top of the blood-cell column and may be removed with many blood-cells by very careful "skimming" by means of a small capillary pipet fitted with a rubber nipple. Place the blood skimmed as suggested on a slide and spread either for a thick film

or for a thin film, according to which is desired. Stain and examine as described above.

For a description of the parasites as found in the blood, *see* page 571. For the interpretation of laboratory findings in the diagnosis of malaria, *see* Diagnosis.

2. *Urine*.—In persons who have malaria but who are resisting the infection sufficiently to prevent clinical symptoms, no change in the urine can be recognized. This is especially true in the tertian and quartan form.

Polyuria during and just preceding the paroxysm is the rule with all mild or ordinary cases of malaria. The fever stage is accompanied and followed by highly colored urine, usually reduced in quantity. It is probable that this is the result of the fever and sweating, as it is also produced by fevers and sweats caused by other diseases. Dead-erick⁵ states that there is a polyuria of convalescence—"post-malarial polyuria." He says further, "The polyuria of convalescence ordinarily begins from three to six days after the attack and continues for from a few days to several weeks."

The output of urea is increased in malaria as in other fevers. There is usually an excess of iron present, especially following the paroxysm.

In mild cases of malaria, albuminuria is relatively infrequent. On the other hand, in severe cases and especially in pernicious malaria, albumin is usually present in varying quantities. Generally speaking, the more severe and more pernicious cases show the largest amount of albumin.

Casts are not often found in mild cases, but in the severer and especially in the pernicious cases both hyaline and granular casts are often present. As would be expected, the more albumin the more casts, in most instances.

It is true that casts and albumin are present to some extent in almost every case of comatose malaria, but this does not indicate that the coma is due to uremia. It is produced in an entirely different manner.

In hemoglobinuric fever most important and significant changes are found in the urine. The individual whose urine, only a few hours previously, was clear, with little or no albumin and casts, will have a chill. The first urine voided afterward will vary in color from light claret to coffee black. When examined in a thin layer by transmitted light it appears of a lighter red color. When examined in a thick layer it may be as dark as black coffee. The hemoglobin is in the form of methemoglobin, though oxyhemoglobin is later formed. Chemical examination shows the presence of hemoglobin.

Albumin is present in varying but usually in very large quantities. The albumin content is not due entirely to the presence of blood, but there is acute nephritis, which increases the quantity of albumin over what would otherwise be present.

Microscopic examination reveals a great deal of sediment and débris resulting from the inflammatory process in the kidney. Some blood-cells are usually found, but they are not present in sufficient numbers

to explain the color nor to justify the diagnosis of the condition as hematuria. It is not a true hematuria but a hemoglobinuria. Casts are present, usually in large numbers, and there are many granular and epithelial casts, indicating the most destructive form of nephritis. There is nothing that impresses one with the true nature of the condition and with its gravity more than does an examination of the urine sediment, especially in those cases in which no great amount of urine is eliminated. One realizes that the tubules of the kidneys are simply plugged or stopped up and that there is great danger of suppression, which occurs in most of the fatal cases of hemoglobinuria. Sometimes the anuria lasts for several days before death. In rare cases, after a few days of anuria, the elimination starts up again, but patients seldom recover if the anuria lasts more than twelve or twenty-four hours.

In cases of hemoglobinuria which end in recovery, and also in pernicious cases in which there are albumin and casts, these continue to be present for several days or weeks, gradually decreasing until they finally disappear entirely, except in a few instances in which the nephritis continues. This probably occurs only in those individuals who for some reason or other are especially prone to the development of nephritis. Some of them would sooner or later have developed it without the influence of the malaria attack.

3. *Stomach Contents.*—The stomach contents are not affected in ordinary cases of mild malaria. On the other hand, in severe attacks, especially of pernicious malaria, the functioning capacity of the stomach may be greatly reduced or almost absent. Stomach tests are not made under these circumstances, but if they were, the total acidity and free hydrochloric acid would be found to be greatly reduced. Slow or imperfect gastric digestion would also be in evidence.

In pernicious malaria, especially in the gastric form, vomiting is a frequent symptom and the vomited material lacks its normal acidity.

In hemoglobinuria, the gastric contents almost always give a reaction for occult blood, and upon microscopic examination are found to contain blood-cells. In many pernicious gastric cases there is sufficient hemorrhage into the stomach, as a part of the general process, to give rise, in case of vomiting, to the so-called black vomit, resembling that of yellow fever.

4. *Feces.*—There is no change in the feces of persons who are infected with malaria but who have no clinical symptoms, nor is there any demonstrable change in ordinary, mild cases of malaria. In pernicious cases, especially in the intestinal form in which the normal function is very largely hindered, the feces are liquid as a symptom of the diarrhea.

In hemoglobinuric fever the feces almost always give a reaction for occult blood, and in the severer cases there is frequently a great deal of blood or hemoglobin present.

5. *Transudates and Exudates.*—In long standing, chronic cases of malaria in which there is great enlargement of the liver and spleen, there is frequently more or less ascites. The fluid is of a dark yel-

lowish color considerably darker than the fluids seen in ascites from other conditions.

6. *Milk*.—Malaria has no effect upon the milk except that in the most severe forms the flow is greatly reduced or entirely stopped. No examination is made of milk in connection with malaria.

7. *Tissue*.—No tissue examination is made for a diagnosis of malaria except that of material obtained by spleen puncture, which will be discussed under Special Examinations, Spleen Puncture. Sections of tissue from any part of the body would show malaria pigment in the endothelial cells lining the capillaries, but this is not made use of in diagnosis because of the convenience of the very much more practical blood examination. Sections of skin in all chronic cases of malaria, especially if cachexia is present, show malaria pigment. This is what gives to the skin its characteristic appearance in malaria.

SPECIAL EXAMINATIONS.—1. *Functional Tests*.—In ordinary cases of malaria the renal functional tests would show nothing. In fact, they are not resorted to in diagnosis in connection with malaria. However, in all cases of malaria, especially those in which there is renal involvement, there is great reduction in the elimination by the kidneys.

2. *X-ray Examinations*.—X-ray examinations are not indicated nor practiced in malaria. It would be possible to demonstrate the enlargement of the spleen and liver by this means, but it is much easier to do so by the usual methods of physical examination, especially palpation and percussion.

3. *Spleen Puncture*.—Puncture of the spleen and microscopic examination of the material obtained has sometimes been resorted to in examining for malaria. There is considerable difference of opinion as to whether or not this method is justified. The author agrees with the advice of Craig¹⁹ that this procedure should not be resorted to for the purpose of diagnosing malaria. It is a dangerous and unnecessary procedure. There is always the possibility of tearing the capsule by a sudden movement while the needle is in the spleen and in such event a dangerous hemorrhage may occur.

Diagnosis.—CLINICAL HISTORY.—There is perhaps no disease in which the clinical history is of more value in indicating the diagnosis than it is in malaria. It is not possible to make an infallible diagnosis without the confirmation of all other evidence by the demonstration of malaria parasites. It is, however, possible, in many instances, to make about as certain a diagnosis on the basis of the clinical history as in any other disease. This applies, however, only to the simple, ordinary cases of malaria, especially in the intermittent form. The clinical history does not help much in the diagnosis of malaria infection in individuals whose illness does not assume the usual clinical forms, especially in those who are malaria carriers but have no clinical symptoms whatever. The following are some of the more important points in the clinical history that may indicate malaria:

(a) *Residence*.—The individual who lives in a region or locality well known to be malarious or one who has lived in such a region dur-

ing several years preceding the attack is likely to have malaria, but if he has lived entirely away from a malarious region for more than one or two years without having had attacks during the time, this is strong indication that the disease present at the time is not malaria. Those who live in the country in malarious regions are much more likely to have malaria than those who have lived in cities and large towns, because there is not much transmission of malaria except in the rural districts.

(b) *Family History*.—It may seem strange that family history should play any part in the diagnosis of malaria, but it is of some value. Of course it is of minor importance compared with the laboratory findings. When the patient is living with his family, members of which have recently had attacks of malaria, he is especially likely to have it himself.

(c) *Occupation*.—A history of an occupation which would lead to special exposure to malaria infection would tend to support a diagnosis of malaria in the presence of other evidence. For instance, persons engaged in logging at a camp or mill where malaria is known to be prevalent, or engaged in work on streams and in swamps where the conditions for the transmission of malaria are most favorable would be much more likely to contract the disease than those whose occupation did not expose them to the same extent. Therefore, the history of such an occupation would tend to support or indicate the diagnosis of malaria.

(d) *History of Previous Illness*.—The history of previous attacks of malaria or attacks of diseases in which the diagnosis was not made but which were probably malaria tend to indicate the presence of this disease at the time of examination. Malaria relapses are so frequent as to make a positive history of previous attacks especially indicative.

(e) *Present Illness*.—Those who have acute or active clinical malaria give about the most clear-cut history of any disease that we know. Chills and fever, intermittent and periodical, occur in more than 50 per cent. of all cases of clinical malaria. Practically all cases of the tertian type who are really sick have chills followed by more or less fever for a few hours, and later by a period of normal temperature. There is no other disease in which the characteristic intermittent, periodical chills and fever occur. Quotidian, tertian and quartan clinical types are all characteristic. The remittent fever produced sometimes by quartan but nearly always by estivo-autumnal infection is much more difficult to recognize by the clinical history of the illness. The attack may begin with a chill, but continue with intermissions for days without another chill occurring. Malaria should always be suspected in such cases unless there is some other very clear explanation of the condition.

One striking thing about the history of attacks in malaria is the fact that almost all malarial chills occur during the day. It is extremely rare for a malarial chill to occur at night. A chill occurring during the night, therefore, is almost certain to be due to some disease other than malaria. A few years ago, during an epidemic of yellow fever

in a town (Tallulah, Louisiana) in which malaria was also quite prevalent, the author was impressed with the importance in diagnosis of the history of the time of day at which the first chill occurred. Of course the physicians did not depend upon the clinical history alone in making the diagnosis, nor as a means of eliminating malaria in suspected yellow fever cases. Yet it was striking how frequently this data enabled them to differentiate between the two diseases, after the appearance of the first chill, before making the microscopic diagnosis. The first and only chill in yellow fever occurs at night in a large proportion of the cases, and the first and all other malarial chills nearly always occur during the day.

Although there are many other diseases in which one or more chills may occur, followed by elevation of temperature, it should be a rule with all physicians that a chill and fever, the cause of which is not apparent, call for a blood examination for malaria as well as for other examinations.

PHYSICAL FINDINGS.—During the first few days of a malarial attack a physical examination may fail to reveal anything that is diagnostic or strongly indicative of malaria. After the disease has lasted for more than a few days, more or less pigmentation or muddy discoloration of the skin and tissues takes place. This is due to the phagocytosis of malaria pigment by the endothelial cells of the capillaries. It is only in the cases in which there are a great many parasites present that this is at all noticeable.

In the hemorrhagic form of malaria one frequently recognizes the lemon yellow tint of the skin and mucous membranes. It is usually very striking in the severer cases.

The tongue is broad and furred in most cases of acute malaria. There are so many other diseases in which the tongue has the same appearance that this condition can be of little diagnostic value.

In chronic cases of malaria the liver is usually somewhat enlarged, but this is not of much diagnostic importance because of the fact that the same thing occurs in a great many other diseases and conditions.

Enlargement of the spleen occurs in a large majority of all chronic cases of malaria where clinical symptoms are produced. However, many people are infected with malaria for months or years without having any demonstrable enlargement of the spleen. Those who suffer from frequent clinical attacks have a spleen that is palpable below the costal border or even much further. The diagnostic importance of an enlargement of the spleen is reduced by the fact that whenever malaria has been sufficiently active to cause much enlargement, the clinical history is usually so definite and clear-cut that the diagnosis is strongly indicated. Malaria should always be suspected and looked for, however, in the presence of an enlarged spleen.

LABORATORY FINDINGS.—The only way in which an exact and absolute diagnosis of malaria can be made is by a microscopic examination and the demonstration of malaria parasites in the blood. The clinical

history may indicate malaria, physical findings may also indicate it, but no absolute diagnosis can be made until parasites have been demonstrated in the blood. Barring extremely few rare exceptions, whenever the patient has sufficient malaria parasites to give rise to clinical symptoms, the parasites can be demonstrated in the blood by competent examination. These rare exceptions are usually cases in which only one chill has occurred, the parasites not always being demonstrable until after the second and sometimes even the third chill.

Malaria parasites can be diagnosed with absolute certainty by one who is familiar with them, and whenever they are found it always means that the patient has malaria. It does not, however, necessarily mean that malaria is the cause of the illness present at the time. Other diseases may be complicated with malaria or occur in individuals who have malaria infection, as well as in other persons. It may occur and does occur that malaria carriers who have few parasites and who show no clinical symptoms at all suffer from other diseases; yet blood examination may show the presence of malaria parasites. There is a tendency for the parasites to produce malaria symptoms in addition to the symptoms of whatever other disease co-exists, although up to that time the patient has shown no malarial symptoms whatever. It is quite possible for one to be misled by such a case in which the malaria parasites are quite numerous and malarial symptoms are added to the other clinical features of the case. On observing such a case for the first time, one would perhaps be likely to overlook the accompanying disease unless it happened to be one in which the symptoms were prominent and characteristic.

In interpreting a negative laboratory examination for malaria in persons who have clinical evidence of the infection, one must not overlook the misleading influence of quinin. Many patients, especially those living in malarious regions, have already taken quinin before a physician is consulted, or it may be that quinin has been prescribed by the physician before the blood examination is made. Large doses of quinin cause the disappearance of asexual parasites in from twelve to about seventy-two hours in all cases of malaria, provided the dose is large enough. This is true of all forms of malaria except, occasionally, the pernicious cases, especially those which have been comatose.

The asexual parasites may continue to appear in the blood for four or five days in rare instances after quinin has been started. The gametes in tertian and quartan malaria usually disappear rather rapidly, usually within three or four days after quinin treatment has been begun. The gametes of estivo-autumnal are more resistant to quinin, and are probably little affected by it. It usually takes from one to two weeks of treatment for all of the organisms to disappear. It is not likely that new gametes are produced after large and proper doses of quinin have been administered, but it takes from one to two weeks for the estivo-autumnal crescents to die out after the patient starts taking sufficient quinin to prevent the production of others. The fact that malaria parasites are not so likely to be found in cases of malaria in which quinin

has been administered as in those in which none has been given, is no argument against the examination of the blood whenever malaria is suspected. Parasites are usually present as long as clinical symptoms continue. Given a patient with fever or chills and fever due to malaria, it is almost certain that there are parasites in his blood. Quinin causes the disappearance of clinical symptoms, usually earlier than it does the disappearance of parasites. Whenever an examination is made under these circumstances a positive examination is of just as much value as if the patient had not taken quinin, but a negative report is not of anywhere near as much negative value as it would be if quinin had not been taken.

Complications and Association with Other Diseases.—So far as the writer knows, there is not a single disease the presence of which prevents the presence also of malaria. Therefore malaria may be complicated by or associated with any other disease or condition to which man is susceptible. The diseases which are most likely to complicate or be associated with malaria would naturally be those diseases which are most prevalent in that particular region in which it occurs. Individuals who have malaria may have pneumonia, tuberculosis, typhoid fever or any other disease, but since malaria is a disease found most commonly in warm countries, it is more likely to be complicated by other diseases especially prevalent in the warm climates, such as, for instance, hookworm and other intestinal parasite diseases. Whatever diseases are associated with malaria do not occur because of the presence of malaria, but incidentally or coincidentally with it.

Other diseases do not greatly alter the course of malaria except that their symptoms may mask the symptoms of malaria to such an extent that it is overlooked. The possibility of malaria being associated with other diseases in any region where malaria prevails to any great extent is so great that, in the author's judgment, a blood examination for malaria is indicated in practically all acute sicknesses. There is no other way of definitely proving that malaria is not present. In fact, a negative blood examination only shows that there is no active malaria present at the time. Whenever malaria is associated with other diseases, the treatment, so far as malaria is concerned, is not altered in any way, except that in special instances quinin may possibly be objectionable. A case will rarely occur, however, where quinin is more harmful than malaria.

Surgical operations, injuries, childbirth, etc., are likely to cause the development of acute malaria in individuals already infected. The development of fever in such cases in regions where malaria prevails always demands a blood examination for malaria. In the event that the disease is present, the choice between quinin treatment and malaria is usually not difficult to make.

The author wishes to mention one complication, not because of its great frequency, but because it often misleads the physician as to the effect of treatment. He refers to the chills, fever, sweats and leukocytosis sometimes produced by inflammation or necrosis of tissue due to

injections of quinin. The inflammation or necrosis may be due entirely to the action of the drug and not to infection. Symptoms usually begin from four to seven days after the injection and vary in severity and duration with the damage done to the tissues. Often the physician mistakes them for active symptoms of malaria and erroneously concludes that the quinin treatment has failed to relieve the active symptoms of the disease. This complication only occurs where treatment by injection of quinin is practiced and fortunately there seems now to be a tendency at least to use the method less than formerly. It is to be hoped that the reform in this direction will continue.

Sequelæ.—There are no sequelæ in ordinary cases of clinical malaria or in the case of malaria carriers who never develop clinical symptoms, provided proper treatment is carried out. Chronic malaria in which the patient has repeated attacks of considerable duration, and pernicious malaria of whatsoever type, including especially hemoglobinuria, are the forms in which there may be sequelæ.

It is stated that *myocarditis* frequently occurs as a result of attacks of pernicious malaria, and this is especially to be expected in the hemorrhagic form. The *myocarditis* may last for a considerable time, accompanied by the usual symptoms of lack of compensation, etc.

The *enteritis* or *dysentery*, in the pernicious cases in which there is especial collection of the parasites in the tissues of the gastro-intestinal canal, is likely to be more or less chronic, regardless of the disinfection of the individual. These symptoms remain as sequelæ for many years. Although they may not be present at all times, provocation may bring them on from time to time.

Cirrhosis of the liver as a sequela of malaria is rare in the southern states, and probably everywhere else where malaria is of the similar mild type, especially where there is sufficient intelligence to lead to considerable use of quinin. On the other hand, in the tropics, where many persons have chronic malaria and malaria cachexia for months and years, cirrhosis of the liver is said to be much more frequent. It seems reasonable that such would be the case.

There is perhaps more or less *nephritis* during the acute stage of all pernicious cases of malaria. It is much more marked in the hemoglobinuric form, in which the *nephritis* is frequently sufficient to cause complete suppression of urine. The tendency is toward rapid recovery, but this is perhaps less frequent in the hemoglobinuric cases. In some instances it continues in a chronic form as a sequela of the disease. Amyloid degeneration may also be a renal sequela.

Neuritis and *paraplegia* have been attributed to malaria and may possibly sometimes be produced by it. It is more likely that in most instances they are simply associated conditions. Seven years ago the author observed a case of hemiparesis which occurred coincidentally with an acute attack of estivo-autumnal malaria. The hemiparesis cleared up in four or five days after the temperature returned to normal as a result of quinin. Most of the effects upon the nervous

system tend to rapidly clear up after quinin treatment is instituted, and they are not likely to remain as sequelæ.

Amaurosis and blindness sometimes occur during attacks of malaria and remain indefinitely. There is some difference of opinion as to whether these are due to the effects of malaria or to the quinin treatment for the disease. There can be no question that quinin is, in certain rare instances, quite damaging to the optic nerve, producing end-vasculitis of the nerve-vessels. There may be more or less permanent thickening and atrophy of the visual path. Davis²⁰ says that "the original effect is upon the vasomotor centers, producing constriction of the vessels. Later the changes take place in the vessel walls." "Degenerative changes also have been noted in the ciliary ganglion. The drug seems to have a selective action upon this part of the nervous system." In view of the fact that quinin is capable of producing a profound effect upon the nerve supply of the eye, it is difficult to determine whether the blindness following malaria is due to the malaria itself or to the quinin. The author has never seen a case of blindness following malaria whether treated with quinin or not.

Herpes labialis and also *herpes zoster* frequently occur in malaria, but it would probably be better to speak of them as symptoms or complications than as sequelæ.

Leukemia has been observed to follow malaria and has in some instances been thought to be caused by it. However, there are many cases of leukemia that certainly occur independently of malaria, and it is quite likely that in those cases following malaria the occurrence is simply a coincidence and that the leukemia is not a sequela.

Postmalarial anemia is frequently considered a sequela of the disease. It is true that the anemia sometimes lasts for many weeks or months and sometimes for a considerable time after the patient has been disinfected of malaria parasites. The anemia following attacks of malaria of moderate severity which has been properly treated rapidly clears up. However, in the chronic cases, and especially in those in which cachexia has developed, the restoration of the blood to normal is very slow. In such cases polychromatophilia and anisocytosis and stippling are often present for months after the patient has begun taking sufficiently large doses of quinin. Nucleated cells are also often present. In the author's opinion the longer the duration of chronic malaria, the longer the time required for complete restoration of the blood.

Cachexia is perhaps the most important sequela of malaria. It is not that it occurs so frequently, but that it is so important when it does occur. Acute cachexia can hardly be considered a sequela of malaria, but chronic cachexia, the usual form, is a sequela of chronic malaria. It is found where the severe forms of malaria are endemic and is almost always produced by estivo-autumnal infection. It is said to be much more common in the white race than in the negro, and also more frequent in males than in females. The following description of malarial cachexia is taken from Deaderick:³

"In this condition the parasites have obtained undisputed possession of the host. The defensive forces have been completely conquered, the blood-making organs can no longer meet the demands made upon them, and toxins, unopposed, work changes, often irreparable, in important organs. Cachexia has been classified as dry or humid, according to the absence or presence of anasarca, and as acute or chronic. Acute cachexia is characterized by a rapid onset and development of symptoms, and usually follows acute malaria, occasionally after only one or two attacks. These cases are infrequent. Chronic cachexia, the usual form, is a sequela of chronic malaria.

"Malarial cachexia is found where the severe forms of malaria are endemic. It may be stated as a general rule that the frequency of cachexia among the white race is an index of the prevalence of grave infections. It is much more common in the white race than in the negro. While negro children are not infrequently the subjects of malarial cachexia, it is much rarer in the adult negro. Of adults, males are more commonly cachectic than females; among children the proportion is about even. The condition rarely develops in persons of the better class, but is seen in those living under improper hygienic conditions, who neglect the treatment of acute malaria.

"Cases of cachexia developing without preceding malaria have been reported, but are subject to question. The malaria may have been unrecognized, as might happen with latent or masked infections. In regions where kala-azar is endemic it is only recently that this disease has been differentiated from malarial cachexia. Infections with the estivo-autumnal parasites are followed by cachexia much more frequently than tertian and quartan infections.

"The cachectic usually presents a singular appearance. The emaciated limbs are in marked contrast to the big belly, and the features are aged beyond the years. The most pronounced phenomena are the anemia and the enlarged spleen. The red blood-cells may be reduced to seven or eight hundred thousand per cu.mm. The leukocytes are generally normal in number or a little below. Numerous differential counts have shown a relative increase of the large mononuclear elements. The red cells may show basophil degeneration, polychromatophilia, poikilocytosis, and nuclei, but none of these changes are by any means constant. According to my experience parasites are rarely found in the peripheral blood. The spleen often extends to the umbilicus and to the crest of the ilium, sometimes beyond. It is usually hard and the anterior border presents a sharp edge. Pain and tenderness on pressure are not always felt. Occasionally a bruit is to be detected over the splenic area.

"The pulse is small, compressible, and may be irregular. Palpitation of the heart and hemorrhages, especially epistaxis, may occur. An anemic murmur over the precordia is often heard. Myocarditis and dilatation are not infrequent. The breath is short, sometimes amounting to actual dyspnea. A cough is common and signs of bronchitis may be elicited. Pulmonary edema is a late symptom.

"The temperature may be normal or subnormal for long periods,
VOL. III.—39.

though evening rises are often observed. Typic paroxysms are not frequent. Fever often follows imprudences. Whether the fever of cachexia is due directly to parasitic activity or to organic changes is not definitely known. The appetite is generally poor and the digestion tardy. Epigastric pain, nausea, and vomiting may be complained of. The tongue and oral mucous membrane are pale. Diarrhea and dysentery frequently occur. Meteorism is common. The liver is usually somewhat enlarged at first; later it may become atrophic. Ascites is not a rare manifestation. When fever exists the urine is ordinarily scanty and highly colored. Delayed development of the genitals is common in the young and diminished sexual power is not rare in the adult. Indifference, intellectual torpor, somnolence, headache, and vertigo are observed in cachectics. Resistance to cold is lessened and rheumatic pains are experienced. The skin is pallid, dry, and rough, and may exhibit sores or purpuric spots. Anasarca may supervene."

Clinical Varieties.—Many clinical varieties, or types, of malaria have been described. The classification is usually based upon more or less arbitrary lines and in many instances serves but little purpose. The symptoms that may be produced in different individuals by malaria infection of one kind or another are frequently so greatly altered by individual circumstances or conditions that each variety or type may quickly change into another. The most useful purpose which this classification may serve is to indicate whether heroic treatment is urgent or whether the usual routine treatment is all that is necessary. Microscopic examination of the blood will determine this very much better than any clinical classification that can be made. This applies especially to the question of whether quinin should be given intravenously or whether the case justifies waiting for the somewhat slower action of the drug given by mouth. Although such a classification may not be of great service, it will probably be well for us to discuss briefly some of the varieties or types.

MALARIA INFECTION WITHOUT RECOGNIZABLE CLINICAL EVIDENCE OF ITS PRESENCE.—If blood examination is made of all the individuals living in a community where malaria prevails, it is found that not only are malaria parasites found in those who have active malaria or who have had it during the few months previous, but that a good many others are infected who have not any recognized symptoms of the disease at the time of examination, and who have not had any for many months or years previous to the examination. Of the 6,664 persons found to be infected out of 31,459 examined in Bolivar County during 1916-17, 44.91 per cent. had no recognized symptoms and had not had any during the twelve months previous to the blood examination. There is a great deal more malaria of this variety or type than is generally supposed. It is true that many of such infected individuals may carry their infection latent and at some later date develop a more active type. At the same time, many others, perhaps the majority, finally lose their infection without even having active malaria.

CHILLS; CHILLS AND FEVER.—Paroxysms of intermittent malarial

fever are nearly always ushered in by a chill. This is especially true with older people and less so with children. The younger the child, the less likely it is to have recognized chills. Children less than two years of age seldom have them. Tertian malaria is much more uniformly characterized by chills than either quartan or estivo-autumnal. Even tertian malaria, however, is not always accompanied by definite chills. In a region where there is a great deal of malaria many people speak of it as "the chills" and not as chills and fever. Although they always have fever following a chill, the fever is not as clearly recognized by laymen as the chill is. Chills, or chills and fever, do not occur in remittent malarial fever except perhaps at the beginning of the attack.

INTERMITTENT MALARIAL FEVER.—Intermittent fever may be of the quotidian, tertian or quartan type, paroxysms occurring every day, every second day or every third day respectively. Quotidian fever may be caused by two crops of either tertian or estivo-autumnal or by three crops of quartan parasites segmenting on alternate days. Tertian fever may be caused by one crop of either tertian or estivo-autumnal parasites. **Quartan fever is caused by one crop of quartan parasites.**

The fever lasts from an hour or two to several hours and may or may not be ushered in by a chill. The intermission in the quotidian type is usually considerably longer than the fever period. There is an intermission of more than one full day in the tertian type. In the quartan type there is an intermission of more than two full days.

REMITTENT FEVER.—Remittent malarial fever is not as frequent as was formerly supposed. At one time many other diseases, like typhoid, paratyphoid and other infections, were classified as malarial remittent fever. In fact, unfortunately too much of this confusion occurs even at the present time. The increased use of laboratory diagnosis, however, has very greatly reduced the frequency of this error. Remittent malarial fever does occur and may be produced by tertian, quartan or estivo-autumnal parasites. It is more likely to be produced by the estivo-autumnal, next by the quartan and least likely to be produced by the tertian form. The fact that the tendency of all malaria parasites to reproduce by crops is less marked in the case of estivo-autumnal malaria than in other varieties is supposed to explain the greater frequency of remittent fever in estivo-autumnal infection. Remittent fever is frequently called bilious remittent fever whenever there are gastrointestinal symptoms accompanied by the vomiting of more or less bile.

ACUTE AND CHRONIC MALARIA.—To divide malaria into acute and chronic forms seems hardly necessary. Any case with acute clinical symptoms may be called acute. Those which remain infected but show few active symptoms may be called chronic cases. If there is sufficient reproduction of parasites to give rise to any considerable damage, such, for instance, as anemia, chronic enlarged spleen, or perhaps a moderately increased temperature, it would be especially appropriate to speak of such cases as chronic. **There are many cases of this sort.**

MALARIA RELAPSE.—Persons who have attacks of malaria and who do not undergo sufficient treatment to destroy the infection frequently

have subsequent attacks from time to time, and these constitute malaria relapses. Approximately 50 per cent. of all acute attacks of malaria that occur in a malarious region consist of malaria relapses and not of new infections.

BENIGN AND PERNICIOUS MALARIA.—Whenever malaria is not sufficiently severe to destroy or threaten to destroy the life of the patient, it is usually spoken of as benign, but whenever it reaches a stage of great severity, it is usually spoken of as pernicious malaria. There are certain clinical types which are especially included under this head—the comatose type, the eclamptic type, the algid type and sometimes the bilious remittent type. They are nearly always produced by estivo-autumnal parasites.

In the comatose type the patient has usually had several paroxysms, occurring in the course of recurring acute attacks or relapses, which have been improperly or insufficiently treated. Usually the patient is stricken rather suddenly with a severe paroxysm, perhaps ushered in by a chill, vomiting and rapidly developing unconsciousness. It may be mistaken for such conditions as apoplexy or sunstroke. The temperature is usually high, generally ranging between 103° and 106° F. (39.4° and 41.1° C.). There may be delirium for a time, giving way, however, to more or less complete coma. Unless prompt relief is obtained by the administration of quinin intravenously, death usually occurs. In other cases the patient may regain consciousness and go on to recovery.

The eclamptic type is found especially in children. The patient is seized with violent pains in the back of the head, vomiting and eclamptic seizures. Profound coma usually supervenes, accompanied by very high fever. If such a case is not examined early and prompt treatment instituted, death may occur within a few hours. Blood examination shows enormous numbers of parasites present.

In the algid type, there is profound prostration. The surface of the body is cold. A profuse, cold, clammy perspiration is present and the patient appears to be in a state of complete collapse. The temperature is not high, as a rule, and in many instances it is subnormal. Unless prompt relief by intravenous administration of quinin is afforded, death is likely to occur in a few hours. In many instances, the most heroic treatment fails to save the patient. Fortunately, it is not necessary that this type of the disease should develop. It occurs only in individuals who have had repeated recurrences and is therefore always due to neglect of proper treatment of previous infections.

In the bilious remittent type the patient is usually seized with uncontrollable vomiting and extreme prostration. Large quantities of bile are vomited and the fever usually runs a remittent but high course. Delirium or coma may supervene.

General Malaria Control.—Under General Control will be discussed those measures which may be applied in a given locality or area, large or small, for the purpose of preventing malaria among the entire people. These measures are directed either against the malaria parasites or against the transmitter of them. If we could entirely eliminate mos-

quitoes from any locality the transmission of malaria would at once cease. On the other hand, if we could destroy all the malaria parasites in a locality the transmission would cease, and not only would the transmission cease but there would be no more sickness from malaria. Malaria can be destroyed either in man or to some extent in the other host, mosquitoes.

DESTRUCTION OF MALARIA PARASITES IN MAN.—We may destroy the malaria parasites in the blood of a group of people either as the parasites are introduced into the blood or after infection and multiplication have taken place. The destruction of parasites immediately after their introduction serves as a prophylactic measure so far as the individual is concerned and indirectly also as a prophylactic measure for the community. If correct doses of quinin or other drug taken at proper intervals would destroy malaria parasites as soon as they are injected into the blood by mosquitoes, and if everybody in a given community would take it there would be no further transmission of the disease.

Perhaps the most extensive use of quinin prophylaxis for all people in the community has been made by the Italians, and as a result there has been a great reduction in the prevalence of the disease. Many students of malaria do not appreciate the important part played by quinin prophylaxis in the campaign against malaria in Ismailia. The author was impressed with this when reviewing the literature on the subject, especially an article in the *Annals of Tropical Medicine and Parasitology* by Stephens, in which he gives more or less in detail the antimalaria measures carried out there by Ross, and the effects, resulting in the practical disappearance of malaria. So far as these details indicate, anti-larval measures were not undertaken until after Major Ross' visit in September, 1902, and therefore could not have affected the prevalence of malaria before 1903. In February, 1902, the entire personnel of the canal company was put on systematic prophylactic quinin. It appears that only the workmen were required to take the quinin under supervision, but that it was optional with certain other employees. The number of cases of malaria fell from 476 in 1901 to 85 in 1902, due apparently entirely to the quinin prophylaxis. Stephens says: "To what the extraordinary fall of 2,591 in 1900 to 476 in 1901 is to be attributed is not clear. For although diagnoses made by the 'sisters' of the dispensary may not be accurate, yet if these 2,591 cases of 'fever' were not malaria, we are at a loss to what to ascribe them. . . . It should be added that quinin at this time was given by the 'sisters' to those who came to ask for it, but to what extent it was given, what effect it had, it is impossible to say, unless one accepts these figures as affording the answer."

PROPHYLAXIS FOR THE ENTIRE POPULATION.—A considerable amount of educational work is necessary in order to induce an entire population to take prophylactic treatment. In fact, it is only when malaria is very prevalent and people can be forcibly impressed with the importance of preventing it that they can be induced to take treatment for this purpose. It is one thing to persuade well people and those who have not

had malaria and who, so far as they realize, are not likely to have it, to take treatment, and an entirely different thing to get those who already have malaria to take it for the purpose of disinfection. Where they are under suitable control, as for instance in the case of armies or groups of laborers, it may be practical to require all to take quinin, but with a free-living people who must first be convinced that they need it and whose coöperation must be secured by argument and publicity work, it is not to be expected that 100 per cent. of coöperation can be secured. Therefore 100 per cent. of prophylactic treatment could not be secured even if the remedy were perfect. There will be exceptional individuals who are antagonistic to any public move. There will be others who, on account of idiosyncrasy to quinin and on account of the discomfort it may produce in them, will fail to take it. There are still others who for various reasons may forget or neglect it.

The success of prophylactic treatment with a large group of individuals will depend very largely upon the personal equation or upon the ability of those who undertake it, to carry it out. There are many individuals who have little ability to secure the coöperation of the public in any move. There are others who would be able to obtain the confidence and coöperation of the same people. One who undertakes to carry out the administration of prophylactic treatment in a community should first be familiar with his subject. He should know what malaria is and how it is carried from one individual to another, and he should also not have any doubt that the measures he is advocating will be successful if carried out.

House to house visits and personal contact with the people are very necessary. The visits must be made at frequent intervals in order that the objections that arise in the case of different individuals from time to time may be met and explained away. This close personal touch with the people is also necessary in order to correct any erroneous reports or impressions that would otherwise influence some individuals to discontinue their treatment. In a group of people in a rural community in Arkansas to whom Derivaux gave quinin either for prophylactic or sterilization purposes, only 17.64 per cent. took 100 per cent. of the treatment during the entire period. It is noteworthy, however, that 79.61 per cent. took over 50 per cent. of the quinin issued to them. It is very probable that in most instances, at least, those who took as much as 50 per cent. of their quinin would be disinfected or would be protected against malaria. This would therefore insure a high per cent. of protection. We must remember that in public health work it is not to be expected that 100 per cent. of results will be obtained except in special instances and when work is done on a limited scale. This is especially true where the success depends upon the coöperation of the people themselves.

The follow-up work in communities Nos. 24 and 25 in the author's observations in Bolivar County showed that by repeated visits and by keeping in close touch with the people, about 85 per cent. can be induced to take sufficient quinin to insure protection. There will be some indi-

viduals in every large group who will refuse to take treatment, no matter who works with them, and regardless of almost any other circumstances which may exist.

Prophylactic treatment depends upon the coöperation of the people. As a matter of fact, success or failure depends not so much upon what the remedy will do, as upon whether the coöperation of the people can be secured to a sufficient extent to induce them to take enough of it to obtain the desired results. The writer believes that there is no question in the minds of most of those who are informed on the subject that if people will take it the transmission of malaria can be prevented. The practicability of prophylactic treatment in rural communities or in different groups of people in different localities and different parts of the world depends very largely upon coöperation. Among those people who, on account of lack of information or of prejudice against the use of quinin or for some other reason, are not inclined to take the drug, quinin prophylaxis is impractical. On the other hand, among people who have sufficient intelligence to coöperate and to appreciate the movement, it will be successful in the hands of intelligent and competent workers.

CONTROL OF MALARIA BY DISINFECTION OF MALARIA CARRIERS.—Usually, whenever we speak of quinin prophylaxis we think of taking quinin to prevent infection. There is, however, a more practical and successful method of preventing the spread of malaria by the use of drugs than the one just described. That is, disinfecting infected persons. If we could disinfect every malaria carrier in a given locality so that there were no malaria parasites present, there naturally could be no further transmission of malaria in the community because there would be no malaria parasites to transmit, regardless of the number of mosquitoes that might be present. It is true that new cases might be introduced as a source of infection, but transmission from the new cases would be very slow, and if we could ever carry out antimalaria work by disinfecting malaria carriers to a sufficient extent to eliminate or practically eliminate the disease, any new cases that occur would naturally receive proper and prompt treatment so as to destroy the parasites and prevent any considerable spread of the infection. In fact, the author believes that if the disease can be eliminated or practically eliminated from a country, no matter how malarious it is, by the general use of quinin and plasmochin for the disinfection of all infected persons, there need be no concern as to the subsequent spread of the disease. The population will have been so well informed and so convinced of the importance of proper treatment by the experience and object lesson that any tendency to recrudescence will take care of itself. Relapses may occasionally occur in individuals who take proper treatment, but if almost all the people in the community take proper treatment to disinfect themselves whenever they have malaria, there can be no spread of any consequence.

LOCATING INFECTED PERSONS IN A COMMUNITY.—In order to locate all malaria carriers in a community, a malaria survey must be made, and this must include, of course, everybody in the community. This survey should ascertain the history of recent attacks of malaria and should

also include blood examinations of all who give negative histories. By the studies in Bolivar and Sunflower Counties it was found that in that region, which is supposed to be representative of the malaria section of the Southern States, at least 50 per cent. of all the attacks of malaria that occurred during a year were relapses from previous infections and that not more than 50 per cent. represented new infections. It was also found that people who had attacks of malaria during a given year were most likely to have attacks during the next year (these were, of course, largely relapses) and also that they were most likely to be malaria carriers. Some of them were found upon examination not to have malaria parasites at all times. It was decided, however, that they should all be considered as malaria carriers or as probable malaria carriers and that unless they had had proper treatment, which seldom occurred, they should be given the necessary disinfecting treatment.

All persons who have had an attack of malaria during the twelve months preceding examination should be treated. Usually there is not the slightest difficulty in inducing them to take treatment and to take it properly. As a rule they know they have had malaria and are willing to take the proper treatment to get rid of it. Many of them think they still have it in their systems and they are willing to take the proper treatment in order to eliminate it.

It is desirable to make a proper blood examination of those who give negative histories. As has been pointed out under Diagnosis, blood examination does not find 100 per cent. of the infected people in a group, but it does find a large per cent. of them and especially those who have sufficient parasites to be a source of infection at the particular time. In the vast majority of cases the person who gives a negative history and also a negative blood examination either is not infected at all or has sufficient resistance to throw off the infection without treatment. This is not always true, of course, but the tendency is in this direction, at least. Therefore, those who are carrying infection but who are missed by both the history and the blood examination are few in number and are least likely to be a source of spread of malaria later.

Both those who give positive histories and those who are found positive on blood examination should be given the treatment necessary to disinfect them. Just what this treatment is and the reasons for the exact details will be dealt with more extensively under the head of Medical Treatment, but in any event it should be continued for a period of eight weeks. Proper treatment disinfects more than 90 per cent. of those who take it.

NECESSITY OF ISSUING THE FULL EIGHT WEEKS' TREATMENT AT ONE TIME.—It is much better to issue the full eight weeks' treatment at one time than it is to issue it in divided quantities. In our Mississippi Delta work, where the quinin alone was used in 10 grain doses daily, the method was adopted of issuing bottles of 112 tablets to those who take tablets and eight ounce bottles of syrup of yerba santa containing the necessary amount of quinin to those who take syrup. It is best to explain to the patient at once that it is necessary for him to take the entire treatment

in order to be sure of eliminating the infection. If the entire treatment is not furnished at one time, it may happen that for some reason or other the part that is furnished will give out before the balance is supplied. Perhaps the most important reason for giving the full treatment at one time is to impress the patient that this is the minimum that is required to disinfect him, and to create the general impression among the people that in the future malaria must be treated by a full eight weeks' treatment if disinfection is to be accomplished. Perhaps the greatest drawback to disinfection has been the insufficiency of the treatment employed. The treatment ordinarily prescribed by doctors does not disinfect the patient, largely because there is no definite fixed duration of treatment impressed upon the patient at the outset as being necessary. Many doctors simply prescribe sufficient treatment for a few days, and even although they intend to repeat or continue the treatment they fail to impress the patient with the absolute necessity for continuing it for a sufficient length of time. The patient feels well in a few days and does not see the necessity of taking treatment any longer and therefore, of course, discontinues it. On the other hand, if we issue the full treatment at once and at the time of furnishing it explain to the patient carefully and thoroughly that nothing short of the full eight weeks' treatment is likely to be successful, we impress him and we are much more likely to have his coöperation.

INTERMITTENT VERSUS DAILY TREATMENT FOR DISINFECTING MALARIA CARRIERS.—The advantages of the daily administration of quinin over intermittent treatment is discussed in detail under Time of Administration. There are sufficient advantages in favor of it so that there is, in the author's judgment, no question whatever that it is the proper treatment. It must be granted that if intermittent treatment is continued sufficiently long it may prevent relapses during the period of administration, but the author is quite convinced that the daily quinin treatment is much more efficient in disinfecting infected persons. He has come to this conclusion after considerable research and investigation and with reluctance, after having once held the opposite view. At that time, however, his opinion was based more upon theoretical grounds than upon actual observation and research.

A very important advantage that the daily administration has over the intermittent is that the treatment is less likely to be forgotten and neglected. Those who take a dose of quinin or other drug every night before retiring soon establish the habit of taking it and are less likely to forget and to neglect it than those who try to take it on one or two days a week.

THE EXTENT OF MALARIA CONTROL THAT CAN BE ACCOMPLISHED BY DISINFECTING INFECTED PERSONS.—In the experimental treatment of the infected among 31,459 persons in Bolivar County during the years 1916 and 1917, there appeared a reduction, as indicated by reëxamination of the blood, of 35.52 per cent. This includes all of the experimental groups, some of whom were treated in a manner that, it is now known, could not have greatly reduced their malaria. In one community in which

a reëxamination was made exactly twelve months from the time the first examination was made and treatment was furnished, the second examination showed a reduction of 83.32 per cent. in the amount of infection. In Sunflower County during 1918 this method of malaria control by disinfecting malaria carriers was carried out under more ideal conditions and more as a demonstration than as an experiment. In the second community examined, in which 432 were surveyed and treated in 1918, a resurvey in 1919, exactly twelve months from the previous one, shows a reduction of 95 per cent. in the prevalence of malaria during the twelve months following the treatment as compared with the preceding twelve months. This is based upon the histories of attacks of malaria. The work here shows that it is possible to prevent the transmission of malaria in a given locality or area by disinfecting infected persons, and also that it is possible to induce the class of people living in the Mississippi Delta region to take the necessary quinin to disinfect themselves.

Now with plasmochin, which tends to destroy and sterilize the gametocytes very quickly and shortens the period necessary to keep up treatment, no doubt better results can be obtained. Cure of the infected people in a given community is still a promising method of malaria control. Four chinoplasmin (quinin 0.125 gram, plasmochin 0.005 gram each) tablets daily for a period of two weeks would be much simpler and probably more effective than the former method with quinin alone.

Prevention.—GENERAL MOSQUITO CONTROL MEASURES.—Mosquitoes are to be controlled almost entirely by preventing the development of larvæ—antilarval measures. Such measures are usually conducted on a community basis, but they may be carried out by individuals in suitable localities.

(1) *Elimination of Breeding-places.*—Mosquitoes spend the larval stage in water. If there is no water suitable for *Anopheles* to breed in, there is no development of *Anopheles* larvæ. *Anopheles* breeding-places can be eliminated either by **filling** so that water does not stand at all, or by **drainage**. Artificial containers sometimes serve as breeding-places and should therefore receive attention. The drainage of mosquito breeding-places will depend very largely upon the particular locality. The most practical method of draining should be followed in each instance. Generally speaking, either filling or permanent drainage construction is to be recommended. Temporary work soon loses its effectiveness unless constantly cared for, whereas permanent work, especially filling, when once properly done requires no further attention.

(2) *Oiling and Poisoning.*—In those collections of water that cannot be filled or drained, oiling may be resorted to. It should always be done with the knowledge that it is a temporary measure. The best method of applying oil is by means of sawdust saturated in the oil. Usually a mixture of about equal parts of crude **petroleum oil** and **kerosene** is most satisfactory. Waste **motor oil** is useful for this purpose and often may be obtained at very little cost. Sawdust soaked in this way may be carried by means of buckets or other containers and

scattered, especially at the edges of breeding pools. The sawdust continues to set the oil free for some time after it is put into the water and it is a much more satisfactory method of ensuring a proper spread than the spray pump or other means. To be of service the film of oil must entirely cover the area in which the larvæ are to be killed. It kills them by suffocation. They are not able to project their breathing tubes through the thin film of oil on the water.

Poisoning by means of different larvacides and sometimes by waste from manufacturing establishments like, for instance, **niter cake**, is also successful. It is very limited in its application, however, because of the danger of poisoning animals and possibly human beings. Another serious objection to any other kind of poisoning is that it kills the predatory insects and also the fish which destroy larvæ. As long as the water remains poisoned, it of course makes little difference if all fish and predatory insects are killed, but as soon as it is replaced by fresh water, or when the poison in the water is removed or neutralized, there is a more favorable breeding-place than ever. Pools of water that can be **stocked with fish** may be kept free from larvæ in this way. The pool must be kept **clear of floatage**, trash and débris and also of weeds, if the fish are to destroy the larvæ.

Collections of water that cannot be drained or oiled effectively can be kept free of larvæ by thoroughly and frequently cleaning them of débris and floatage and also by keeping the banks perfectly clean.

(3) *Clearing*.—*Anopheles* larvæ breed most freely in collections of water that are more or less covered by vegetation such as grass, weeds, trees, etc. Not only are such collections more suitable for breeding, but the adult mosquitoes are protected from their enemies by the vegetation. **Clearing the land of vegetation**, especially of trees, is a very important factor in the control of *Anopheles*. In a large part of the malaria section of this country there are many bayous, ponds and streams in which mosquitoes breed in large numbers. These are usually uncleared. The custom is to clear the high ground for cultivation or other developments but to leave the low ground of these places uncleared. *Anopheles* come out from such swamps or weeds to attack their victims and then return to the swamp for protection and also to breed. A very important factor in malaria control is clearing and then pasturing the land bordering the bayous, lakes and streams. Usually it makes excellent pasture. The author believes that he can say with perfect confidence that if the bayous and streams of Sunflower County, one of the heavily infected counties of the Mississippi Delta, were all cleared and well pastured, malaria would practically disappear from the country and a considerable profit would also result from the use of these pastures.

During the past few years a number of demonstrations in malaria control by antimosquito measures have been made by the United States Public Health Service and by others. A report of malaria control at Hamburg, Arkansas, by Taylor is illustrative of what can be done by a concentrated effort in mosquito control. In this instance no major

operations were undertaken or necessary. Proper training of ditches, filling of unnecessary pools, etc., were carried out. The results of the work are strikingly shown in the accompanying chart (Fig. 16). The per capita cost of this work was \$1.45.

The most extensive malaria control work ever carried out was done during the war by the United States Public Health Service in the extra-cantonment zones in fifteen different states in the United States. Le-Prince stated that the entire area in which *Anopheles* control had been accomplished was over twelve hundred square miles. "Where cantonments were located in notoriously malarious sections very little malaria was contracted by enlisted men, and the malaria sick rate among enlisted men in camp was very much lower than it would have been had they stayed at home. The commanding medical officers at the cantonments report mosquitoes as being scarce at nearly all camps, and *Anopheles* as being seldom seen, except at two of the aviation camps near rice field areas." The cost of drainage, oiling, supervision, equipment and transportation averaged about \$1.80 per acre of territory controlled.

There is no longer any question as to whether malaria can be controlled in this way. The question is whether people desire to do it. With sufficient funds and the desire, there is nothing to prevent practical elimination of *Anopheles* and incidentally of malaria from almost any locality.

(4) *Personal Protection Against Infected Mosquitoes.*—An individual may protect himself against malaria infection either by not allowing the parasites to be introduced into his blood or by killing them after they are introduced.

Protection against infection may be summarized as protection against the bites of infected mosquitoes. An individual's chief interest should be to **avoid being bitten by mosquitoes** that may be infected, but he may also indirectly, for his own protection, influence the number of infected mosquitoes that are in his immediate surroundings. For instance, if an individual is a member of a family or of a household or group of people among whom there are one or more persons who have malaria, he can contribute very largely to his own protection by influencing those who are infected to disinfect themselves. This will be explained more in detail in another part of this article. The malaria-bearing mosquitoes that become infected in a given house tend to return to the same house and to infect others there instead of going to other buildings. Therefore, whenever one is living with a group of people, in a malarious section, he should exert any influence he has to induce every person who has malaria to take proper **treatment** to cure his infection. A man who is familiar with the treatment necessary to disinfect infected persons and can impress others with its necessity has a valuable means of reducing the danger of infection to himself.

In addition to this, he should also encourage in any way that he can the proper protection of known malaria carriers from mosquito bites until they are disinfected. It is of great importance that malaria car-

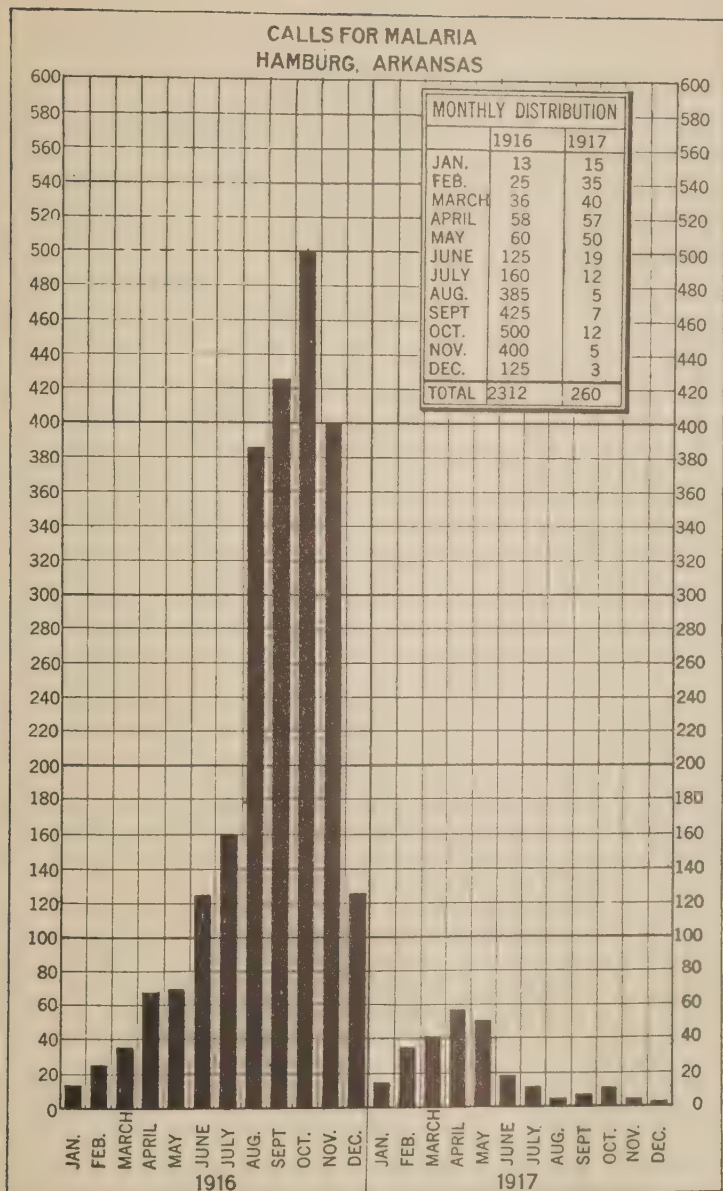


FIG. 16.—CALLS FOR MALARIA, 1916 (estimated) and 1917, HAMBURG, ARKANSAS. Population 1,285. Office, hospital and residence calls included (Taylor, Southern Medical Journal).

riers in a given group of people should be protected against mosquito bites. Since the *Anopheles* feed especially at night, the chief protection needed is during the night. Sleeping in well screened rooms and also under well arranged **mosquito nets** becomes therefore of great importance. The length of time that a malaria carrier is likely to remain a potential source of infection while taking proper treatment varies very greatly in different individuals and with different species of parasites. Since we have no way of knowing who the exceptional cases will be, and since in many instances it is not known which species of parasites is present, the safest thing is for all persons known to be infected with malaria to be especially protected from mosquito bites for a period of at least two or three weeks.

Protecting oneself against the bites of mosquitoes is more direct and effective personal prophylaxis. In intensive malarious sections it is almost impossible to screen out mosquitoes so thoroughly from residences as to furnish absolute protection. Unless, however, *Anopheles* are very abundant and there is a great deal of malaria present in a locality, one may protect himself by staying in well screened houses during the *Anopheles* biting time. Although under exceptional circumstances *Anopheles* will bite during the daytime, they bite so much less frequently then than they do at night that practically all the transmission of malaria takes place at night and there is extremely little danger during the daytime. One should protect oneself from sunset to sunrise and need not fear infection during the day. Not only is it necessary to have the living and sleeping quarters well screened, but one must avoid going out, especially to other residences and to other places where infected people have been and where there are likely to be infected mosquitoes present. Public gatherings at night are especially likely to be a source of infection. To protect oneself, it is necessary to keep one's quarters well screened and to stay behind the screens during the proper hours. Whenever an individual deviates from this rule, he reduces his chances of avoiding infection to a corresponding extent.

Individuals may protect themselves to a greater or lesser extent by sleeping under well arranged and efficient mosquito nets, even though they are obliged to sleep in houses or camps in which there are infected mosquitoes. A large part of the infection with malaria takes place while the victim is asleep. Bed nets should be used in all instances where the screening of the house is not thorough and well maintained.

Chemoprophylaxis.—There has been great difference of opinion expressed as to the value of quinin prophylaxis. Until the advent of plasmochin, this was the only prophylactic drug available. Many observers have obtained almost 100 per cent. of efficiency from this means alone, whereas others have claimed to observe frequent failure or poor results from quinin. The author gets the impression that in the vast majority of cases where results have been unsatisfactory or imperfect, the fault has lain chiefly with the method of prophylactic treatment. Frequently, also, the statements of unsatisfactory results are made without care and accuracy. It often occurs that an observer states that he gave quinin

to everybody in a given group of people and that in spite of this much malaria developed. Upon further reading it is often found that the dose employed was insufficient or that the treatment was not systematically administered for sufficient period of time following the last exposure.

The Italian method of administering quinin for prophylaxis is by daily doses, and Celli gives the following table of the results of its general use in this way, showing the reduction in the cases of malaria in the Italian army:

TABLE 5.—RESULTS OF QUININ PROPHYLAXIS IN THE ITALIAN ARMY. (*Celli*.)

Year	Number of Men	Attack Rate	Recidivates	Primitives	Observations
		Per cent.	Per cent.	Per cent.	
1902	199,253	27.44	21.41	6.03	
1903	206,468	24.14	17.85	6.28	Begun quinin prophylaxis.
1904	210,637	19.21	12.71	6.50	Continued quinin prophylaxis.
1905*	218,409	21.52	13.04	8.48	Do.
1906	211,245	18.99	12.67	6.32	Quinin prophylaxis extended.
1907	202,320	12.46	7.96	4.50	Do.
1908	216,679	8.04	5.19	2.85	Do.
1909	228,951	6.96	4.72	2.24	Do.
1910	234,104	5.10	3.23	1.87	Do.
1911	233,517	4.90	3.04	1.86	Do.

* Year of periodical recrudescence of the epidemic.

The reduction of malaria as a result of this quinin prophylaxis is shown in Table 6, which gives the new cases in the hospital of Taranto. The evidence is sufficient to show conclusively that quinin prophylaxis has a great effect in reducing the prevalence of malaria in a group of people, and therefore that it has a similar effect in preventing the disease in individuals.

In our Bolivar County, Mississippi, experiments all the people living in each of two communities, containing a total of 1,657 people, were subjected to daily quinin prophylaxis. The dose was 5 grains (0.324 gram) for adults and $\frac{1}{4}$ grain (0.016 gram) for each year of age for children. This was kept up for from three to five months. During that period there was great reduction in the prevalence of malaria, but a number of cases of malaria occurred in persons who had previously had attacks. The author was quite convinced that the dose employed, namely 5 grains (0.324 gram) a day, was not sufficient to prevent recurrences in every instance, *i.e.*, not sufficient to prevent recurrences of attacks in some of the malaria carriers.

The same sized doses and the same method of administration of quinin is necessary for prophylaxis as is necessary to cure the infection following an attack of malaria. In fact that is just what is accomplished with quinin. Quinin does not prevent infection, as has been supposed.

Neither does it have much if any effect upon the parasites during the incubation period. This period averages about fourteen days but may be as long as twenty-one days or even longer. Unless quinin is continued at least a week or two beyond the incubation period following the last exposure, it usually fails to prevent an attack. It is the common experience that, notwithstanding the absence of clinical malaria during the period of exposure, if quinin is stopped as soon as exposure ceases, clinical attacks usually occur in due course of time. Therefore quinin is not an effective prophylactic against infection but it is a means of curing the infection after the expiration of the incubation period. The proper dose and method, whether taken during the period of exposure or afterward, is the same as that required to cure the infection under other circumstances, *viz.*, 10 grains (0.65 gram) quinin sulphate daily (preferably at night) for adults and corresponding doses for children.

Plasmochin is destined to take the place of quinin as a prophylactic for malaria. While quinin has little if any effect upon malaria parasites during the incubation period, plasmochin, on the other hand, has profound effect upon the parasites in this stage and in fact prevents infection where the patient is under its influence at the time of inoculation, and provided it is continued for at least a few days following the inoculation.

S. P. James and his co-workers have shown in a most convincing way that plasmochin effectively prevents mosquito-borne malarial infection in healthy individuals, while quinin lacks this remarkable property.

While considerable further research and experience may be required to determine the proper doses and method of using plasmochin as a prophylactic, enough is already known to warrant its use when required covering short periods of great danger of infection.

Daily doses of 0.02 gram and 0.04 gram are effective. Larger doses are unnecessary. There is no necessity to combine quinin with the plasmochin for this purpose as it is desirable to do in treating the disease. Plasmochin in these doses can be continued safely for two weeks or longer at a time. There is some doubt as to whether it can be safely continued over long periods of time without intervals of at least a few days being allowed for rest periods. For the present, this should be advised.

One who is obliged to do so may travel and live in malarious regions without danger if he will simply take the proper amount of quinin or, better now, plasmochin. Not only is this so, but in those instances where it is necessary to send armies or groups of laborers or others into malarious regions for different purposes, it is perfectly practicable and feasible to prevent the havoc that would otherwise be wrought by malaria by systematically giving quinin or plasmochin. Any individual who cares to protect himself may do so in this way.

GENERAL MANAGEMENT.—The general management of cases of malarial fever is not different from the management of other fevers. The patient should be **put to bed** and should remain in bed for from forty-eight to seventy-two hours. In the pernicious cases, of course, the period

TABLE 6.—RESULTS OF QUININ PROPHYLAXIS IN THE HOSPITAL OF TARANTO.

Year	New Cases		Observations
	Total	Per cent. of men	
1900.....	193	20.19	
1901.....	130	13.19	
1902.....	35	14.64	
1903.....	81	8.33	Begun quinin prophylaxis.
1904.....	89	9.65	Do.
1905*.....	107	10.09	General quinin prophylaxis.
1906.....	72	7.00	Do.
1907.....	74	6.75	Do.
1908.....	46	3.94	Do.
1909.....	23	1.25	Do.
1910.....	13	.75	Do.
1911.....	21	.96	Do.

*Year of periodical recrudescence of the epidemic.

in bed should be longer than this. The bowels should be emptied, preferably with a **purgative**, although **enemata** may serve the purpose. In all severe cases, especially in children, it is of great importance at first to wash out the bowels and also to give a purgative as soon as it can be done. Some believe that simple **saline purgatives** are as good as any, but others strongly advocate the use of **calomel**. In the author's judgment, in every case in which the diagnosis of malaria is reasonably certain, calomel should be given, followed in a few hours by the saline. There is good reason for the belief that calomel is superior to any other purgative in malaria. Although the author strongly advocates the use of a purgative, calomel by preference, at the beginning of all cases of acute malaria, he wishes to be clearly understood as opposing any delay in the administration of the specific drug, **quinin**, or **quinin and plasmochin**, while waiting for the action of calomel or other medicine. Specific medication is always to be begun in malaria as soon as it can be given after the diagnosis is made. The mistake is often made of giving calomel or some other purgative and waiting for it to act before starting specific treatment. This is not only a serious mistake, but in the case of pernicious malaria, it may frequently result in the death of a patient who could otherwise have been saved. An instruction frequently given by physicians who visit malaria patients is to give a purgative, wait until it acts and then begin quinin. If, for some reason or other, the purgative is slow to act there may be a delay of several hours or even of a day or two before the patient is given the life-saving specific remedy, all this time having been lost in waiting for the action of other drugs that have no specific action.

After the acute attack of malaria has passed and the temperature has returned to normal, the patient may be allowed to get out of bed and, as soon as he is strong enough, to resume his usual occupation. It is not necessary to keep patients in a hospital or at rest while convalescing from malaria, except of course following severe or pernicious

attacks. In such instances the condition of the patient will indicate when he is able to resume work. The important thing is to give proper instruction as to treatment before discharging the patient from the hospital, or allowing him to leave his bed.

It is very important that all malaria patients should sleep in well screened houses or under suitable bed nets, or both, in order to keep out mosquitoes.

DIET.—In acute malaria the first thing to do is to empty the alimentary canal and at the same time administer quinin. The second important thing is to **avoid a heavy diet** of any kind. Generally the diet should consist of liquids for a day or two, or even longer in pernicious cases. During convalescence and the period of treatment necessary for disinfection, the patient should have the usual diet but should avoid overeating and especially refrain from eating large quantities of indigestible food. In regions where malaria is very prevalent, there is a common belief that such things as muscadines, unripe watermelons and green fruit will cause chills and fever. They do not actually cause chills and fever, but they do precipitate attacks in people who are already infected. They favor the development of malaria parasites and the production of clinical attacks and should therefore always be avoided by those who are known to be infected.

CLIMATOLOGY.—A climate which favors the production of *Anopheles* mosquitoes favors the spread of malaria. Great variation in the temperature, especially if changes are sudden, tends to produce attacks in people who are already infected. Sudden chilling of the surface of the body by getting wet while hot, etc., tends to produce attacks in those who are already infected and to make the disease worse in those who are having clinical symptoms. Regardless of these facts, it is not necessary for any person to leave a malarious country in order to get rid of malaria infection nor to go to a high, dry climate to recover from malaria. Given proper specific treatment, one should be able to recover from malaria in the most intensely malarious spot in the world.

Climate, or at least elevation, seems to have some effect upon the development of clinical symptoms and upon recovery from an attack. It frequently occurs that persons who have gone for months and perhaps for years without having attacks while living in a low, warm, malarious region soon develop a chill or an acute attack of malaria when they go to a higher altitude. Usually, also, the chill that occurs under these circumstances is more severe than previous ones have been. A few days of treatment give prompt relief, and it is noteworthy that many such persons lose their infection without continuing treatment for any great length of time. Although as indicated a moment ago, resort to special localities and climate is not necessary in any case, it is a fact that patients are usually cured of their malaria more rapidly in high altitudes than in lower ones.

LOCAL TREATMENT.—There is no local treatment indicated for malaria except perhaps for the chronic enlarged spleen of long duration, in which counter-irritation by means of **red iodid of mercury ointment**

has been recommended. The author is frankly of the opinion that experimenting with such methods tends to cause neglect to the specific remedy, and that it should perhaps never be resorted to. There is great doubt whether it has any efficacy whatever.

TREATMENT OF SYMPTOMS.—The fever is sometimes sufficiently high, 104° to 106.5° F. (40° to 41.4° C.), and the headache and suffering so great as to justify and demand treatment to relieve them. The **coal tar preparations** are useful, and although there is considerable objection raised to their use, the harm or possible harm is certainly outweighed by the relief they afford the patient. It is not necessary that large or objectionable doses should be given.

The nausea and vomiting that occur with acute attacks of malaria are best relieved by **calomel**. In the pernicious cases, especially in those of children who have convulsions, **reducing the temperature** by baths and cold enemata is indicated.

SPECIFIC THERAPY (VACCINES AND SERUMS).—There is no excuse or scientific basis for using or trying to use vaccines or serums in the treatment of malaria.

MEDICINAL TREATMENT: SPECIFIC DRUGS.—Malaria is one of the diseases for which we possess a specific remedy. All that is required to obtain 100 per cent. of results is the proper use of **quinin** or **quinin combined with plasmochin**. Barring moribund cases or those in which too much damage has already been done, there are practically no exceptions. There are as many methods of treating malaria as there are authors who have written on the subject. No endeavor will be made here to describe the methods that have been advocated by different authorities, but the author will give what in his judgment is the most practical and correct treatment, based upon a study of the treatment advised by different authorities and also upon rather wide experience and opportunity for observation.

Up to 1926 we had one and only one specific remedy for malaria—quinin and other alkaloids of cinchona. There have been literally hundreds of remedies besides quinin advocated and promoted for malaria. It would be useless to discuss them here, for all can be put down as of little or no value.

Notwithstanding the enthusiasm with which many different remedies besides quinin have been advocated from time to time, all of them have gone the same way, into disuse, with the exception of one—**plasmochin**—introduced in 1926.

The introduction of plasmochin marks the beginning of a new era in the history of the treatment of malaria. Here we have a specific remedy that has already stood the test in the hands of hundreds of investigators throughout the world and has been found to have definite and profound specific effect upon malaria. The most ardent supporters of quinin only, in the face of the facts, now have to recognize that in plasmochin we have a specific remedy for malaria which actually has certain points of superiority, as well as some of inferiority, over quinin. Those who, through caution and conservatism or otherwise, have refrained from

the use of this new remedy and adhered to quinin alone, sooner or later will have to recognize and take advantage of the merits of plasmochin as a valuable adjunct to quinin in the treatment of malaria.

The author has been reluctant to accept and indorse plasmochin, largely because of the extravagant claims, especially of superiority over quinin, that were made by early advocates of its use and because of the variable and sometimes high toxicity of the drug, in doses first thought to be necessary. Larger experience with plasmochin by so many competent observers throughout the world, smaller doses and using it in combination with quinin have established a useful place for it in treatment and especially in prevention of malaria. The limitations of its usefulness and best methods of application have hardly been determined as yet, because so short a time has elapsed since its introduction. However, enough is already known to make it available for practical use.

It will be convenient to discuss the treatment of malaria with quinin alone and then take up the use of plasmochin.

Quinin.—(1) *Dosage.*—The dose of quinin used in the treatment of malaria should be sufficient to kill the malaria parasites in the blood without injuring the patient. There are parasites lodged in the organs and tissues of the body which are entirely out of reach of quinin for the time being, no matter how large the dose may be. All that we can hope for is to kill those that are in the free circulating blood, and we can really only hope to kill the asexual parasites at that. Ten grains (0.65 gram) of quinin are sufficient to destroy the parasites that are present in the blood during the time that the maximum concentration of the drug is present. Five grains (0.324 gram) are not sufficient. Much larger doses than 10 grains are no more efficient. The larger the dose of quinin, the more discomfort produced. Some people can take 30 or 40 grains (1.95 or 2.60 grams) during a day without great discomfort and some can even take as much as 90 or 100 grains (5.85 or 6.50 grams). Few people are made very uncomfortable by 10, 20 or 30 grains of quinin per day, especially if they remain in bed or at rest. The author's own feeling is that 10 grains are the proper dose for adults and that it should be repeated as often as necessary to obtain the proper amount of quinin during a twenty-four hour period. He does not believe that 10 grains in one dose should be exceeded at any time. This is especially true of intravenous administration, as well as of administration by mouth. If there is ever any reason for the use of quinin intramuscularly, the dose should not exceed 10 grains. It may be repeated as frequently as is necessary to administer the required quantity.

(a) *Proportionate Dose for Children.*—It is usually said that children can take quinin better than adults and that they should have proportionately larger doses. In a large series of experimental treatments of malaria to disinfect malaria carriers in our Bolivar County work we gave $\frac{1}{2}$ grain (0.0324 gram) for each year of age up to twenty years and then the 10 grain (0.65 gram) dose. An analysis of results from this treatment showed that there had not been the same proportion of disinfection in children as in adults. From the data in hand we were

able to calculate what dose would be required to disinfect as large a per cent. of children as were disinfected by 10 grains in adults. That is as follows: under one year, $1\frac{1}{2}$ grain (0.0324 gram); one year, 1 grain (0.065 gram); two years, 2 grains (0.13 gram); three and four years, 3 grains (0.195 gram); five, six and seven years, 4 grains (0.260 gram); eight, nine, and ten years, 6 grains (0.40 gram); eleven, twelve, thirteen and fourteen years, 8 grains (0.52 gram); fifteen years or older, 10 grains (0.65 gram).

(2) *Mode of Administration.*—Barring pernicious cases in which there is reason to believe that the patient's life depends upon getting it into the blood stream at the very earliest possible moment, quinin should always be given by mouth. It is slowly absorbed, the maximum quantity reaching the blood stream in about eighteen hours, but a considerable concentration is present in two hours after its administration.

In pernicious cases where it is thought necessary that the quinin should reach the blood stream at once, intravenous administration may be a life-saving measure. In that instance, not exceeding 10 grains of bimuriate of quinin dissolved in not less than 20 c.c. of normal salt solution should be administered at once. A large, all glass syringe is the proper apparatus for this purpose. One who is competent can give the injection in this way almost as easily as hypodermically. Intravenous administration of any drug, especially quinin, is quite a formidable procedure and should never be resorted to except where it is absolutely demanded. There is no excuse for the administration of quinin intravenously for the routine treatment of ordinary malaria, and the use of this method for this purpose can only be condemned.

(3) *Time of Administration.*—Different authors have advocated the administration of quinin at certain times, with special reference to the occurrence of chills. The advice is wrong. The time to begin administering specific treatment for malaria is promptly after the diagnosis has been made. As soon as the physician knows that he is dealing with a case of malaria nothing should prevent beginning the use of quinin at once. He should not wait for the action of a purgative, nor for the fever to go down. He should not wait for a certain time preceding the next paroxysm, but should begin quinin at once. In treating acute attacks of malaria about one dose every eight hours should be given for the first three or four days without regard to anything except the object of administering the desired amount during the twenty-four hour period. Thirty grains (1.95 grams) during twenty-four hours are sufficient for all cases, barring perhaps extremely rare pernicious cases. In pernicious cases it is proper to give a dose of quinin intravenously and to repeat the dose every two or three hours until 30 grains have been administered. Not a single dose should be given intravenously, however, after the patient is able to take quinin by mouth. In the most severe pernicious cases not more than two or three doses should be given intravenously at the short intervals of two or three hours. After that it should certainly not be repeated oftener than every eight hours. It should be

remembered that the most lasting and dependable way of administering quinin is by mouth.

The active clinical symptoms—fever, or chills and fever—are practically always controlled by 30 grains of quinin daily within a period of three or four days. In fact it is rare indeed for these symptoms not to disappear within forty-eight hours. The accuracy of the diagnosis should be questioned in any case in which chills and fever, or fever alone continues more than two or three days. Other causes should be looked for. Complications or incorrect diagnosis is usually found to be the explanation. Quinin is so effective in controlling these symptoms that often much smaller doses bring the same results. Ten, 15 or 20 grains will control the symptoms promptly in most cases. Since we have no way of knowing which cases will require larger doses, it is better to employ the 30 grains daily in all cases where there is no special contra-indication or objection. Where there is any special contra-indication for the large amount, one need not hesitate to reduce to a daily amount of 20 or even 15 grains.

After the first three or four days of 30 grains of quinin a day for acute attacks, the patient should be given only one dose of 10 grains, daily preferably, at night before retiring. Since treatment must be kept up for a period of at least eight weeks, it is desirable that it should be convenient and produce the minimum amount of discomfort. There is much more discomfort produced when the patient is up and about than when he is at rest. A dose of quinin taken at night does not produce as much discomfort, in active patients, as the same dose taken in the morning. It is much more likely to be remembered and taken at night before retiring than at other times of the day.

(4) *Frequency of Administration.*—To insure ample concentration of quinin in the blood stream to kill all parasites in the circulation during the acute stage, it should be administered as often as once every eight hours, but after the acute symptoms have passed it is not necessary to administer more than one dose per day for final disinfection. The drug being slowly absorbed and slowly eliminated, especially in patients whose bowel actions are normal, a sufficient concentration is present in the blood at all times to destroy parasites if one dose a day is taken.

(5) *Duration of Treatment.*—Some people are disinfected of malaria parasites by taking quinin for only a few days. A larger per cent. are disinfected by taking it for two weeks. A still larger number, perhaps about 60 per cent., require four weeks' treatment. The best information the author can obtain indicates that more than 90 per cent. are disinfected by taking quinin systematically for a period of eight weeks. It would probably take between three and four months to disinfect 100 per cent. With these facts before us, it is very apparent that we must strike some middle ground between a very short period of treatment, in which only a small per cent. are disinfected, and the other extreme, the three or four months' treatment necessary to disinfect 100 per cent. The author's opinion is that for routine purposes all malaria

patients treated with quinin alone should be put upon eight weeks' treatment. None should have a shorter period of treatment. By careful inquiry into the history, we can usually recognize a good many of the resistant, difficult cases to disinfect who would comprise the remaining 10 per cent. not disinfected after eight weeks' treatment. Most of such cases give a history of previous treatment followed by relapse. Any case thought likely to be a resistant one and to require longer treatment should be given treatment at the outset accordingly. Two, four or six weeks should be added to the usual eight weeks' treatment. This must be done without intermission. If, for instance, a patient takes treatment for eight weeks and then after stopping, relapses, the full eight weeks' treatment must be repeated and the additional time added to it. The first course of treatment, which failed, is of no value and does not count as a part of the second course. This is a fundamental principle affecting the treatment of any disease by means of a specific, which is not generally recognized or appreciated. To give insufficient treatment and wait for a relapse to indicate whether the patient has been disinfected usually results in necessitating a needlessly long treatment, in the first place, and, in the second place, exposes the patient to whatever danger there may be in repeated attacks of the disease. It is the duty of physicians, therefore, to inquire, in every malaria case, whether the patient has recently had other attacks of which this is likely to be a relapse and whether the treatment employed was of sufficient duration to have been likely to disinfect the patient. If so, he may conclude that this is probably a resistant case and should give treatment accordingly.

(6) *Menstruum*.—The 6, 8 and 10 grain doses of quinin are best given in compressed tablets of 3, 4, or 5 grains each. Tables are more convenient, less expensive and set free their quinin more quickly and more certainly than capsules do. They do not deteriorate with age as is frequently thought. Recently the author secured some quinin tablets from different manufacturers, some of the tablets being as much as seven years old. When dropped in water they crumbled and set free their quinin in a very few minutes. The $1\frac{1}{2}$ to 4 grain doses are best given in aromatic syrup of yerba santa. This menstruum greatly reduces the bitter and unpleasant taste and is perfectly satisfactory. A sufficient amount of ordinary sulphate of quinin should be mixed with the syrup so that one teaspoonful contains the desired dose; or in children under one year of age one-half teaspoonful should contain the desired dose.

Quinin in Solution Condemned.—The author believes that prescribing quinin in acid solution is one of the worst mistakes that can be made in the administration of quinin for malaria. There are extremely few people who will take such a dose for a period of eight weeks. Any doctor who has been in the habit of prescribing quinin in solution or who is disposed to do so in the future should investigate the method by taking a few doses of it himself. He will have to have a lot of grit to keep it up for the period necessary to disinfect a patient of malaria. To

prescribe such unnecessarily unpleasant doses simply defeats the object in view. Nothing could contribute more to the prejudice and objection to the use of quinin than to try to give it to patients in this way.

(7) *Contra-indications.*—There are no contra-indications for the use of quinin in the proper dose for treating malaria, except perhaps extreme idiosyncrasy to the drug. There are some instances in which people are made quite uncomfortable by quinin. In most instances the discomfort consists of ringing in the ears, more or less dizziness and frequently urticaria. Patients under the influence of large doses of quinin feel it very much worse, especially the dizziness, when exposed to heat, as, for instance, if they are working in the field in the hot sun. Usually these symptoms will pass off in a few days if the patient continues to take the drug. The best remedy for the urticaria in patients who are obliged to take quinin is to continue its use. After a few days the effect wears off. It may be necessary for those who are especially susceptible to the drug to take smaller doses for a few days until they can acquire a certain amount of tolerance.

There are many people who imagine they cannot take quinin. This idea is often encouraged by doctors. Patients who say they cannot take it are frequently given quinin disguised in some way and then they do not feel the effect at all. It is much better in the majority of instances to tell the patient frankly that there is no way of masking the unpleasant effect to any extent and that the proper thing is to overcome it by continuing to take the drug. At any rate, he should be informed that it is a choice between malaria and quinin, with the exception that it may be possible sometimes to cure malaria with plasmochin alone. It is usually not difficult for him to make the decision. Doctors ought to refrain from encouraging patients in their fancy that they cannot take quinin. It is especially bad to give hypodermics of quinin to people who fancy that they cannot take it by mouth. It is not practical to give quinin hypodermically or intramuscularly over a sufficiently long period of time to disinfect patients of malaria. Even if it were practicable, it would still be ridiculous to substitute such a painful and formidable procedure for the simple and eminently successful administration by mouth.

(8) *Antidote.*—In cases of poisoning by quinin taken by mouth, emptying the stomach by means of the stomach-tube, vomiting induced by tickling the fauces, or any other method of eliminating quinin from the stomach should be resorted to. In cases of poisoning by overdoses of quinin given intravenously, stimulants, especially **strychnin**, are indicated.

Plasmochin.—(1) *Introduction.*—Plasmochin was first promoted for the treatment of human malaria by Mühlens in 1926. It is a synthetic derivative of quinoline and is somewhat indefinitely stated to be an alkyl-amino-6-methoxyquinoline salt. The resemblance of its chemical formula to that of the quinin group suggested the possibility of its having an effect in malaria. It was first tried on bird malaria by Roehl, who found that doses of 1 c.c. of a 1 to 50,000 solution for each 20 gm. of body weight

definitely prolonged the incubation period of malaria following inoculation in birds.

Plasmochin is especially effective against the gametocytes, which are notably resistant to quinin. The announcement of this fact plus other claims of superiority led to rapid trial of this new remedy by many students of malaria throughout a large part of the world wherever malaria prevails. Favorable reports have encouraged increased trial and use, and further research. Wider and wider experience has rapidly brought to light information as to the value and the limitations of plasmochin. Although much further information is needed, there is already enough established to justify and permit valuable practical use to be made of it in the treatment of malaria.

(2) *Dosage*.—At first, use of plasmochin to take the place of quinin was attempted. This led to the use of maximum doses that often proved toxic and produced unpleasant if not dangerous toxic symptoms. Different individuals vary greatly in their susceptibility to the toxic effect of plasmochin. One person may be severely affected by a dose that produces no untoward symptoms in others, and this increased susceptibility cannot be foreseen.

The toxic symptoms consist of cyanosis, epigastric pain and colic, vomiting, abdominal pain, dyspnea and weakness. These symptoms usually occur after the drug has been administered for several days—a week or more. It seems to have a cumulative effect in most cases, although some especially susceptible individuals show symptoms after the first day or two. Some or all of these toxic symptoms occur in 10 to 25 per cent. of people taking daily doses of 0.05 gram or more. In fact 0.06 gram in twenty-four hours should never be exceeded. When this much is given it should not be continued for more than six or seven days, before stopping for a few days. It should be given in divided doses, usually three per day after meals.

The clinical symptoms of malaria are caused by the asexual parasites. The sexual parasites—gametocytes—are not supposed to cause clinical symptoms but they are responsible for the infection of mosquitoes and possibly have some relation to relapse.

Plasmochin in sufficient doses in many cases causes the parasites to disappear and stops the symptoms in simple tertian malaria and to a less extent in quartan. It has much less effect on the asexual parasites and the clinical symptoms in estivo-autumnal. In fact it is generally necessary to employ toxic doses to affect the clinical symptoms of this form and then it usually fails. Quinin, on the other hand, in proper doses promptly controls the clinical symptoms in all forms of malaria. Therefore there is little reason for employing the much inferior and more toxic plasmochin for this purpose, except in such cases as those in which quinin cannot be used.

Plasmochin has the peculiar property of reducing the number of the gametocytes and of rendering them non-infectious to mosquitoes. Mosquitoes do not become infected by the gametocytes from patients taking even 0.01 or 0.02 gram of plasmochin daily. This remarkable effect

against the more resistant form of the parasite is the greatest virtue of the drug. It does better what quinin does poorly and it does poorly what quinin does better. For that reason the two should be combined.

(3) *Plasmochin combined with quinin*.—Plasmochin was first tried alone for malaria. Failures to control the clinical symptoms without employing toxic doses were so numerous, especially in estivo-autumnal, that the promoters soon advocated combining quinin with it. Results were good of course, when enough quinin was used. The manufacturers put out a "plasmochin compound" tablet containing 0.01 gram plasmochin and 0.125 gram quinin to be taken two tablets three times daily. Further experience indicates that there is no use to give this much plasmochin for its effect upon the gametocytes and as an adjunct to quinin. More recently the manufacturers and the promoters of the remedy in America, Winthrop Chemical Co., have put out another tablet containing 0.005 gram plasmochin and 0.125 gram quinin sulphate. These are to be taken six to eight daily for a period of two to three weeks.

These tablets are marketed under the trade name of chinoplasmin, in bottles containing 100 tablets each.

Children one to five years should take one to two tablets daily; older children three to four tablets daily.

All information indicates that this quinin and plasmochin combined treatment over a period of only two or three weeks cures the infection and prevents relapse (and transmission) as well as or better than a much longer period of treatment with quinin alone in any sized doses. The much shorter period of treatment necessary and the lessened transmission seem to the author to recommend this as the best routine treatment of malaria available at the present time.

SURGICAL INDICATIONS.—The only surgical treatment that has been employed in malaria is **splenectomy** for very large spleens. The operation is probably never demanded or justified in simple malaria. Proper quinin treatment always results in a gradual but certain reduction of the spleen which, however, sometimes requires many months to return to normal size. This is readily understood when we recall the large amount of insoluble pigment deposited in the spleen which must be broken up and removed by a long, slow process.

MANAGEMENT OF CONVALESCENCE.—In cases of ordinary chills and fever no special management of convalescence is required. There is difference of opinion as to whether iron and other tonics should be given. A good many follow the practice of giving some form of **iron** and possibly **strychnin** as a tonic during the convalescent period. Others employ **arsenic**, believing that it has some specially beneficial effect in malaria. In fact, there was a time when it was believed that arsenic was actually curative in malaria. There is no good ground for its use, however, in the presence of the much more certain and beneficial drugs, quinin and plasmochin. The author's opinion is that plenty of fresh air and nutritious food are all the tonic that is needed during the con-

valescence of any ordinary case of malaria. The very severe pernicious cases are sometimes followed by more or less prolonged and tedious convalescence. The anemia that occurs is sometimes very marked, and considerable time is required to rebuild the lost blood. The most important thing of all is to keep the patient constantly under proper specific treatment. One must be guided by the conditions in the individual case as to the duration of rest following attacks of pernicious malaria. Usually in such cases the patient should be kept in the hospital for at least a week or two following a return to normal temperature. Although rest, fresh air and nutritious diet are by far the most important factors in rebuilding the lost blood, the author believes that arsenic, perhaps in the form of Fowler's solution, 5 to 10 minims t.i.d., may possibly be of additional service following exceptional pernicious attacks.

It is the duty of a physician who has the responsibility of a case of malaria, to advise the protection of the patient against the bites of mosquitoes in order to avoid the danger of transmission during the first few days and including the convalescent period. The vast majority of cases are non-infectious after the first day or two of proper treatment.

Prognosis.—As to RECOVERY.—The prognosis of malaria is influenced to such an extent by different factors, especially by the clinical type of infection and the treatment the patient is undergoing, that it is difficult to make any definite statement with regard to it. The types of malaria which occur in some localities where the disease is quite prevalent are seldom fatal provided the patient is given quinin, especially if he receives proper doses. In other localities or countries, the disease is much more fatal, due perhaps to the predominance of the estivo-autumnal parasites, which give rise to nearly all cases of pernicious malaria. It can be stated confidently that practically no malaria patients die except those who do not receive proper treatment or those who are too far advanced before treatment is instituted. It is abundant evidence of incompetency for a physician to lose malaria patients who have been under his care for any considerable length of time.

In a general way, it may be said that the more extensive the use of quinin in the treatment of malaria, the lower the mortality, and that the less use made of quinin, the greater the mortality. In some of the tropical countries, in which conditions for the transmission of malaria are most favorable and where there is little use of quinin on account of ignorance or on account of prejudice against its use, as is frequently the case, the mortality is quite high. In other regions, such as, for instance, the southern part of the United States, in which quinin is rather extensively used for the treatment of all acute attacks of malaria, although frequently not most effectively, and where the conditions as to intelligence, etc., are more favorable, the mortality from the disease is extremely low.

The great variation in the mortality from malaria in different parts of the world is illustrated in Table 7 given by Deaderick.

TABLE 7.—DISTRIBUTION OF MALARIA BY COUNTRIES. (*Deaderick.*)

Author	Locality	Cases	Deaths
Laveran.....	Turko-Russian War.....	140,000	1,092
Laveran.....	Constantine.....	1,310
Laveran.....	Italian Army.....	4,856	13
Schellong.....	New Guinea.....	1,954	22
Ross.....	Greece.....	960,048	5,916
Ross.....	Hong Kong.....	7,352	984
Ewing.....	Camp Wikoff.....	605	39
Smart.....	Civil War.....	1,373,355	15,423
Travers.....	Malay States.....	3,397	348
Terburgh.....	Dutch Indies.....	2,308,128	114,490
Cardamatis.....	Athens.....	22,618	15
Koch.....	Grosseto.....	281
Koch.....	East Africa.....	63	2
Hagen.....	Papua.....	301	23
British Colonial Reports.....	British Colonies.....	12,617	618
Wright.....	British Malaya.....	17,468	680
Haw.....	Baberton.....	449	14
Hope.....	North Bengal.....	1,784
Laveran.....	Algiers.....	98,774	7,432
Gorgas.....	Panama.....	1,055	5
Erni.....	Dutch Indies.....	116,879	731
United States Marine Hospital.....	General.....	6,618	20
Various Hospital Reports.....	Southern States.....	1,294	30
German Protectorate Reports.....	German Protectorates.....	5,003	32
Malaria Society.....	Italy.....	22,792	120
		5,109,001	148,049

This table indicates an average mortality of 2.89 per cent. for the different parts of the world represented. That it may be far from dependable is indicated by a comparison of definite information as to the mortality in Sunflower County, Mississippi, with the stated mortality of the southern states, of approximately 2.3 per cent.

Sunflower County, Mississippi, a few years ago showed almost as great a prevalence of malaria as any other county in the southern states. The incidence is about equally divided between the tertian and the estivo-autumnal type. The physicians of the county reported an average of 8,236 cases per year during the five-year period 1914 to 1918 inclusive. A careful survey in which the history of attacks of malaria during 1917 was obtained from 8,053 persons and computed for the county indicates that 21,756 cases occurred during one year (1918). Blood examination of those who claimed not to have had attacks of malaria showed that a considerable number of those who gave negative histories showed malaria parasites in their blood. The average number of deaths from malaria in Sunflower County during the four-year period 1914 to 1917 inclusive was 77 per year. If we base our calculation upon the number of cases treated by physicians, this indicates a mortality of 0.93 per cent. If we base our calculation upon the number of cases indicated by the history of attacks obtained as in our survey, this indicates a mortality of 0.35 per cent. This is certainly the maximum mortality rate from malaria in Sunflower County, which it is believed is a representa-

tive locality of the malaria area of the southern states. That it is still somewhat lower than this seems very certain if we include in our calculation those who had malaria parasites in their blood but were not recognized as having the disease because of lack of recognized symptoms, and base our calculations upon the sum of the total number of persons who had attacks of malaria and of those who had parasites in their blood without having had attacks that were recognized. We may conclude from these facts that the mortality from malaria in Sunflower County, which is probably as high as in almost any other part of the southern states, is less than 0.35 per cent. of those who have the disease or infection. There are not many persons in this particular locality who have been disinfected of malaria by quinin treatment, but almost all who have attacks take quinin in some form or other sufficient to relieve or modify the attack and to prevent death. No doubt if quinin were entirely withdrawn from the locality the mortality from malaria would be increased many fold in a comparatively short time.

Not only is the prognosis influenced very largely by the treatment malaria subjects receive in different localities, but it is also influenced greatly by the type of malaria which prevails. In any locality where tertian malaria, due to *Plasmodium vivax*, is the chief or only type present, there would be very few deaths from malaria. The same is true to a large extent with the quartan type due to *Plasmodium malariae*. Few deaths are produced by quartan malaria. On the other hand, estivo-autumnal malaria, due to *Plasmodium falciparum*, is far more destructive than either of the other two. Practically all cases of pernicious malaria are produced by falciparum and almost all the deaths from malaria occur in what are commonly called pernicious cases. The high mortality in pernicious cases is indicated by the instructive table copied from Deaderick (Table 8).

The very great difference in the mortality as reported by the different observers here quoted is no doubt due largely to the difference in classification of clinical types by the different authors. If it should occur, as no doubt it does, that one observer classes as pernicious cases only those of the most extreme type, the mortality would be much higher in his group of cases than it would be in the pernicious cases of another observer who included in the particular classification a larger number of milder cases. There is no hard and fast dividing line between pernicious and non-pernicious cases.

The mortality from malaria in children is considerably higher than in adults except that it is also high in the case of old persons. There is a great variation in the resistance of different individuals to the effect of malaria. Perhaps one explanation for this is the fact that where malaria prevails to a great extent those who are especially susceptible to its destructive effect die while quite young and do not reach maturity. This is confirmed by the fact that in a locality where malaria is very prevalent the adult residents seem to have milder forms of the disease than children, whereas adults who come from non-malarious regions have much more severe attacks, which often, in the absence of

TABLE 8.—MORTALITY IN PERNICIOUS CASES OF MALARIA. (Deaderick.)

Author	Number of Cases	Number of Deaths
Laveran.....	104	53
Bailly.....	886	341
Nepple.....	14	6
Antonini and Monard.....	39	9
Maillot.....	186	38
Grall.....	117	75
Burot and Legrand.....	210	142
Smart.....	16,209	4,164
Travers.....	260	81
Martirano.....	19	9
Pezza.....	2	1
Tanzarella.....	31	8
Thayer and Hewetson.....	3	2
Plehn.....	10	1
Maillot.....	7	6
Theophanidis.....	5	2
Cardamatis.....	3	2
Pampoukis.....	52	20
Billet.....	40	2
Segard.....	24	15
Maurel.....	156	77
Caccini.....	135	56
Matirano.....	6	3
Charity Hospital, New Orleans.....	8	6
Neer.....	3	3
Celli.....	8,032	1,879
Cardamatis.....	50	9
Colonial Reports.....	252	133
Kelsch and Kiener.....	89	51
Albini.....	87	11
	27,039	7,205

proper treatment, result fatally. It may be, therefore, that there is not actually any difference in the destructiveness of the disease in individuals of different ages, provided they have not previously acquired any degree of immunity or resistance by previous attacks. Boyd has recently shown that an attack of malaria caused by one strain of tertian parasites protects for a time at least against infection with that same strain, but it does not protect against other strains of tertian parasites.

Race is also thought to play a part in the mortality from malaria. For instance, in the southern states the mortality rate among the negroes is generally believed to be lower than it is among the whites. A much larger per cent. of the negroes have acquired resistance by previous attacks than is the case with the whites, because the infection is $33\frac{1}{3}$ per cent. greater in negroes. The greater prevalence of the infection among negroes would result in a larger per cent. of immunity or resistance and therefore in a somewhat lower mortality per case or attack.

Certain races are much more prejudiced against the use of quinin than are others. For instance, the Spanish people in Latin America are as a rule very disinclined to use quinin, and it is with difficulty that they can be induced to take it. The author's attention was called

to this very forcibly while he was engaged in research work in the Ancon Hospital in Panama. Dr. Henry R. Carter stated that not only was it practically impossible to induce the Spanish laborers to take quinin after they left the hospital, but that they frequently had to be watched to keep them from throwing away what was given them in the hospital. The solution of quinin was used, it seems, for the purpose of making it more difficult for them to throw it away or to deceive the nurse when it was being administered, as well as perhaps because it was thought that it was more effective. The author is inclined to think that the use of quinin in solution perhaps did more harm than good. There are not many people who will continue to take it for any length of time in this form.

AS TO FUNCTION.—Whenever recovery from malaria takes place, it is complete and usually very rapid so far as function is concerned. Long before the patient is disinfected, he appears to be perfectly well. After pernicious cases, it may be considerably longer before the normal is regained, especially in the case of the spleen and liver. The spleen remains enlarged for many months in those cases in which it has been considerably enlarged, as it sometimes is. With proper quinin treatment, however, the size of the organ reduces steadily, and in from a few months to a year it returns to the normal size. In cases in which there has been a great deal of deposition of pigment in the tissues, it is sometimes a month or two before this has been entirely removed and the complexion has returned to the normal. Large quantities of pigment are present in the spleen for many months after all parasites have been destroyed. However, this does not seem to affect the function of the organ seriously, if at all. The same thing can be said of the liver, except that it contains less pigment and probably clears more rapidly.

Pathology.—The most important changes in malaria are those affecting the blood and especially the red blood-cells. Malaria does not affect the leukocytes to any considerable extent. The only notable change in the leukocytes is an increase in the percentage of large mononuclear cells. This is due to an effort of nature to supply an increased number of cells in order to phagocyte the pigment and perhaps the parasites set free by the segmentation of the schizonts. The increase may run up to 20 or 30 per cent., although in most cases of malaria the large mononuclear cells do not exceed from 10 to 15 per cent. The normal is from 1 to 8 per cent.

In pernicious malaria there is frequently a leukocytosis running as high as 15,000 or 20,000 in some cases. Whenever leukocytosis occurs, it is also accompanied by an increase in the neutrophil count.

Since every parasite, as it matures, destroys at least one red blood-cell and since countless millions of parasites mature at the time of occurrence of every malaria paroxysm, this destruction of red blood-cells soon leads to more or less anemia. Some think that the anemia is out of proportion to the number of parasites present. Lawson has offered observations in support of her belief that the anemia which appears to be out of proportion to the number of parasites is due to the fact that

individual parasites migrate from one cell to another and that a single parasite damages many cells. The anemia is frequently out of proportion to the number of parasites in the peripheral circulation, but the number found in blood smears does not necessarily indicate the number present in the individual.

Most of the malaria parasites in an infected person are lodged especially in the capillaries of certain organs and tissues, but to a certain extent in the capillaries of the entire body. Those which are present in the peripheral circulation are either very young and small parasites or parasites that have temporarily escaped from lodgment in the capillaries. One cannot estimate the number of parasites present nor the amount of blood that will be destroyed by the number of parasites in the circulation.

The anemia is due to a reduction in the total number of cells and a further reduction in the hemoglobin content of the individual cells. The color index is always below normal in uncomplicated malaria.

FINDINGS AT AUTOPSY.—The *skin* of subjects who have died of acute malaria usually presents a dusky, brownish hue which is more pronounced the longer the disease has lasted.

The *spleen* shows the most marked changes, perhaps, of any organ. It is always more or less enlarged. Enlargement is greater in tertian than in estivo-autumnal malaria and it is greater the longer the duration of the disease. The color is grayish and reddish brown. The capsule strips easily in most instances. The organ is usually soft and pulpy. There is enlargement of the malpighian corpuseles, sometimes giving the appearance of sago spleen. The cut surface shows the very much darkened tissue due to the presence of enormous quantities of pigment. Microscopic sections show the large mononuclear cells and giant cells to be heavily pigmented. The malpighian bodies show the greatest quantities and largest masses. The walls of the small vessels are thickened and the lumen is frequently obliterated by enormous numbers of parasites contained free within the lumen as well as within the cells lining the vessel. Smears of pulp from the spleen show large numbers of parasites, red-cell debris and pigment. One receives the impression from studying such preparations and also from studying suitable sections from the spleen that not only are there many dead parasites in the spleen but also that there is growth and development there. In cases dying of some other disease, but which have latent or old malaria infection, the spleen usually shows more or less enlargement and pigmentation, depending upon the duration and extent of the latent malaria. Sections show pigment in the cells and also parasites in the small vessels and possibly in the cells. Frequently parasites can be found by examining smears from such spleens where none could be found in blood-smears during life.

The *liver* is enlarged and congested in all cases in which death is due to malaria. It is usually of a dark or brownish color due to the pigment it contains. Microscopic sections show collections of pigment in the capillaries, which are frequently well marked by its presence in the

endothelial cells and also between the vessel-wall and the adjoining liver-cells. The small blood-vessels are frequently plugged or entirely clogged by the collection of parasites and pigment in their lumen. In the case of patients dying of other disease where latent malaria is present, more or less pigment and parasites can usually be found in the liver, not to the same extent, however, as they are found in the spleen. Cirrhosis is seldom if ever produced by malaria.

The *kidneys* are usually more or less congested, and are softer than normal in the case of patients dying of malaria. The capsule strips easily and the medullary pyramids sometimes show minute hemorrhages. There are usually cloudy swelling and other damage to the endothelial cells lining the convoluted tubules. The cells lining Bowman's capsule are usually not affected. The tubules are frequently more or less plugged with casts. Certain of the capillaries are plugged with parasites and pigment, but to nothing like the same extent as is found to be the case in the spleen, liver and even in the brain.

In the case of patients dying of hemoglobinuria, the kidneys usually show special pathology in addition to that found in ordinary acute malaria. The lumen of the loops of Henle is usually choked with casts of hemoglobin and with endothelial detritus. Since most cases of hemoglobinuria in which death occurs show suppression of urine, the tubules are plugged with casts in almost all cases. Aside from the more intense processes in the kidney and the greater jaundiced or yellowish appearance of all tissues, there is little difference between the autopsy findings in hemoglobinuric fever and those in other pernicious forms of malaria. It frequently occurs, however, that the evidence of parasites is less, but they are always found in malarial hemoglobinuria.

Localization of malaria parasites in the *brain* is one of the chief causes of death from malaria. Frequently at autopsy sufficient pigment is found in the brain to give a grayish or slaty appearance. There is perhaps no organ in which localization of malaria parasites in the capillaries can be as satisfactorily demonstrated as in the brain. The cut surface sometimes appears grayish as a result of the large amount of parasites and pigment present in the capillaries. Smears or contact preparations show capillaries plugged for long distances with parasites, most of which are attached to or within red blood-cells. Some, however, appear to be entirely free from blood-cells. Parasites are found in all stages of development, and in autopsies made soon after death the parasites in such specimens still stain well. No doubt they live for many hours in the cadaver. Cases in which coma or other cerebral symptoms are prominent features show the largest proportion of capillaries obstructed by parasites. As a matter of fact, the coma is produced, in the author's judgment, by the anemia of the brain resulting from the obstruction of large numbers of capillaries. Occasionally hemorrhages and thrombi are found, but these are rather rare. Hemorrhages are probably due to the rupture of obstructed capillaries.

The entire *vascular system* is greatly affected by malaria because of the fact that the development and reproduction of the parasites take

place within it. The endothelial cells lining the entire vascular system destroy the parasites and pigment, but it seems that the smaller the vessels, the more of this takes place. However, in vessels too large to be obstructed, we find that large numbers of endothelial cells lining the walls contain pigment. In most instances where death is due to malaria the capillaries of some vital organ or organs are plugged with parasites and débris from their reproduction. It is this plugging of the capillaries of one organ or another that produces many of the symptoms in pernicious malaria. For some reason or other, the parasites collect in the capillaries of certain organs of an individual much more than they do in others. For instance, in some cases the parasites collect in the brain especially, giving rise to comatose or other cerebral forms of malaria. In other instances the parasites collect especially in the capillaries of the stomach or intestines, giving rise to a form accompanied by prominent gastro-intestinal symptoms, such as nausea, vomiting and diarrhea.

Even the capillaries of the skin contain large numbers of parasites and large quantities of malaria pigment, especially in chronic cachectic cases. This is sufficient in many instances to give rise to the peculiar yellowish or brownish appearance of the skin of severe chronic malaria cases. In rare instances even the cardiac capillaries are plugged with parasites.

In autopsies in hemoglobinuric cases the heart-muscle is frequently soft and flabby and upon microscopic examination is found to have undergone more or less fatty degeneration.

The changes in the *bone-marrow* are among the most striking found at autopsy in acute malaria. The marrow is frequently of a brownish, chocolate color due to the presence of large amounts of pigment. This discoloration depends largely upon the severity and duration of the infection. The pigment consists not only of that present in parasites but also of that retained from the segmentation of other parasites. Microscopic sections show many of the vessels to be plugged with parasites and pigment. Here are found the largest number of developing gametes. In cases of estivo-autumnal infection, gametes show all stages of development, if they are present at all. The macrophages frequently contain large quantities of pigment granules, in many instances as much pigment as would be produced by twenty-five or fifty parasites.

The *lungs* show the presence of a larger or smaller number of parasites and of pigment in the capillaries, in autopsies on cases dying of severe acute malaria. There seems to be considerable variation in the collection of parasites and pigment in the lungs, but these organs do not offer as favorable conditions for the collection of pigment as do other organs and tissues.

Autopsies on cases of pregnancy dying of acute malaria, or on cases of abortion from malaria, usually show very large numbers of malaria parasites in the maternal vessels of the placenta. In fact, a study of the sections indicates that the life of the fetus is destroyed by interference with its nutrition through the plugging of the capillaries by parasites and débris from their reproduction.

The *suprarenal glands* usually contain many plasmodia, pigmented leukocytes, and a few macrophages. Some of the vessels are distended or dilated, apparently as a result of obstruction farther on. Craig says that "a few of the adrenal cells may contain pigment and infected corpuscles."

Historical Summary.—One has only to look at the malaria maps of the world showing how the malaria zone belts the earth to know that its existence goes much farther back than we can trace it historically. The ancient Egyptians were familiar with malaria, according to Groff, and the word "*aat*," which is found among the inscriptions of the temple of Denderah, is believed to refer to malaria. Deaderick says that more than one thousand years before the birth of Christ malaria is mentioned in the Orphic poems. Hippocrates gave a good description and classification of tertian, quotidian and quartan malaria. Plautus, who died in 184 B.C., wrote about what is believed to have been malaria in Italy.

The first important epoch in the history of our knowledge of malaria dates from the discovery of Cinchona bark and its action in malarial fever. Peruvian bark was introduced in the middle of the seventeenth century. Torti and Morton divided the fevers into two classes—those which were cured by the bark, and those which were not. They had in their hands at that time the therapeutic diagnostic test which is used to a very great extent at the present time.

Pelletier and Coventou, in 1820, succeeded in isolating quinin, the most important alkaloid of Cinchona bark.

The discovery of the malaria parasite was made by Charles Louis Alphonse Laveran on November 6, 1880, and announced to the Paris Academy of Medicine, November 28, 1880. It was many years until his work was accepted and among the last countries to accept it was his own—another instance in which "a prophet is not without honor save in his own country." The idea that malaria is disseminated by insects, including mosquitoes, had been suggested from time to time by Koch, in 1884, Laveran, in 1884, Flügge, in 1891, Manson, in 1894, and by Bignami, in 1896. No doubt many others advanced the same idea from time to time, but the fact was finally proved by Ross, in 1898, following the suggestion of Manson. Ross's discovery marks the beginning of a new epoch in the history of our knowledge of malaria, and stands out as one of the most important, if not the most important, discoveries ever made in connection with this perhaps most important disease of the world. Upon his discovery most of the malaria control that has ever been accomplished is based. It has already contributed to the progress of civilization more than can be told.

Deaderick and Thompson did the writer the honor of saying that "Bass's discovery of the method of cultivating the malaria parasites (in 1912) is the most important land-mark in the history of malaria since the discovery of Ross." Whether this proves to be true depends largely upon the use to which the cultivation of malaria parasites *in vitro* may be put in the future. Fortunately the author's work has been confirmed in nearly all civilized countries of the world.

Geographical Distribution.—No description of the geographical distribution of malaria throughout the world that can be made would present the facts in as readable and useful form as would the three maps taken from Mannaberg's studies on malarial disease in Nothnagel's *Encyclopedia of Practical Medicine*. It will be seen that the malaria zone belts the globe and that the disease is more frequent as the equator is approached from each direction (Figs. 17, 18 and 19).

Sociological Aspect of Malaria.—Up to the present time the sociological aspect of malaria has not been properly emphasized. Although it has been appreciated that it is largely a community disease, the extent to which it is a family disease has not received sufficient attention.

MALARIA AS A COMMUNITY DISEASE.—Although mosquitoes capable of transmitting malaria are widespread, their flight and life habits are such as to prevent their transmitting malaria at long distances from their source of infection. A given individual who is a malaria carrier in a community is not likely to be a source of infection beyond from half a mile to a mile from his own residence. In a community where a large proportion of the population are infected with malaria, there are many sources of infection of mosquitoes and therefore there is great probability of its transmission. One who lives in a malaria community runs greater or less risk of becoming infected, according to the number of malaria carriers living in the community. Every malaria carrier in the community is a menace to the health of the community and should be looked upon as such, just as a case of leprosy, small-pox, diphtheria, etc., would be. Since the infection is curable by means which are not beyond the reach of all, there is little excuse for anybody's remaining a malaria carrier. He is an unnecessary source of infection.

The control of malaria on a large scale will ultimately be made a community problem. In communities where it is possible to prevent or control mosquitoes, this can be made a community undertaking. In communities where the difficulties in the way of mosquito control are sufficiently great to make it impractical or difficult to carry out, it is still possible to control malaria by disinfecting the infected persons with proper treatment. Sooner or later those who are interested must know that every malaria carrier in a community is a menace to the health and life of those who live in the community.

Although malaria-infected persons are likely to be a source of infection to all the residents in a community, they are especially dangerous to their own families. A person who has malaria is likely to infect mosquitoes, which, after depositing their eggs and developing their parasites to the infectious stage, are most likely to return to the same house to feed again. In this way they are much more likely to infect other members of the same family than to infect other persons in the same community. If people with a proper sense of responsibility who are infected with malaria realized the danger of transmitting their infection to other members of their own families, causing sickness and perhaps death, they would be much more interested in thoroughly disinfecting themselves than they are at present.

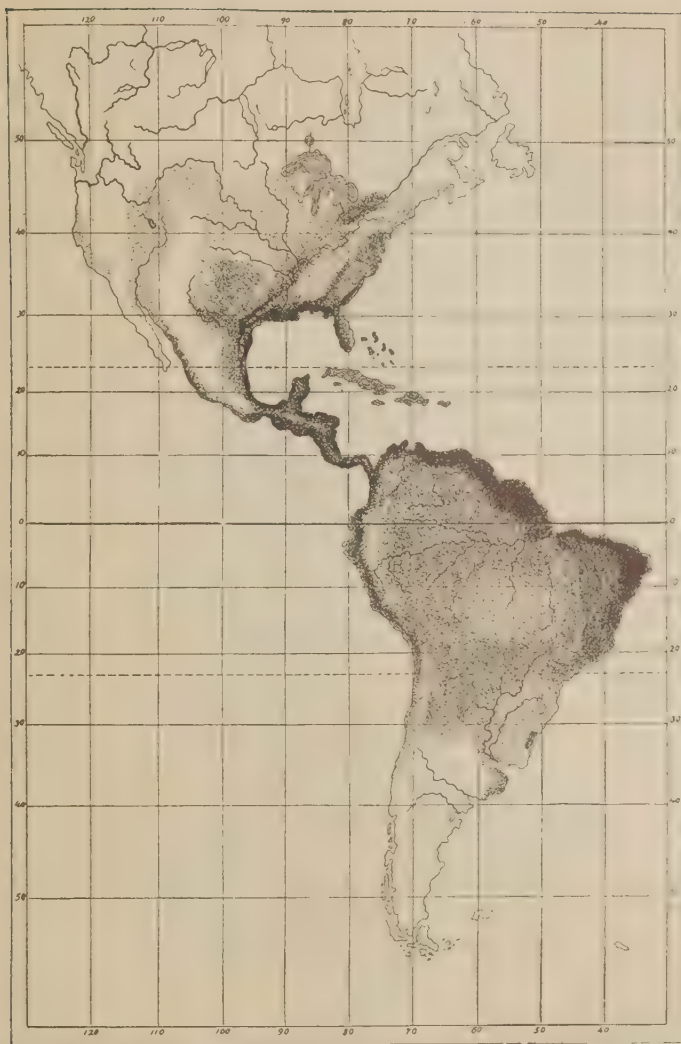


FIG. 17.—SHOWING THE DISTRIBUTION OF MALARIA AS INDICATED BY THE INTENSITY OF THE SHADING. (Mannaberg, in Nothnagel's Encyclopedia of Practical Medicine, W. B. Saunders Co.)



FIG. 18.—SHOWING THE DISTRIBUTION OF MALARIA AS INDICATED BY THE INTENSITY OF THE SHADING.
(Mannaberg, in Nothnagel's Encyclopedia of Practical Medicine, W. B. Saunders Co.)

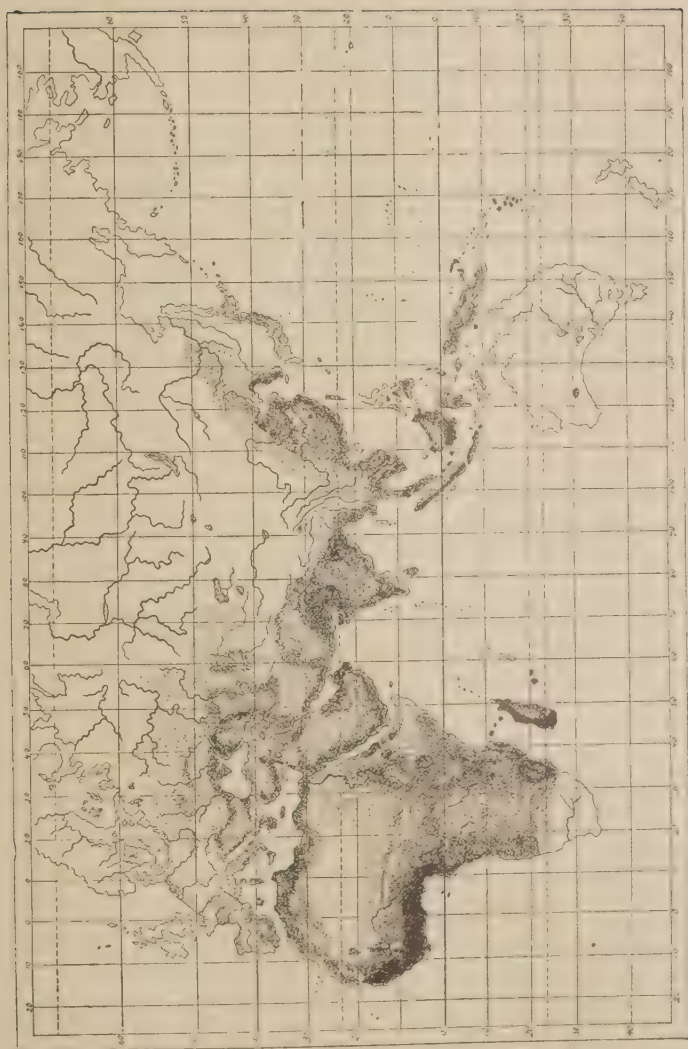


FIG. 19. SHOWING THE DISTRIBUTION OF MALARIA AS INDICATED BY THE INTENSITY OF THE SHADING.
(Mannaberg, in Nothnagel's Encyclopedia of Practical Medicine, W. B. Saunders Co.)

The author believes that this is one of the responsibilities that a doctor who treats a case of malaria should recognize and assume. Not only should the patient be advised and given treatment to disinfect him for his own health, but he should be informed of the great menace he is to the health and life of his family as long as he remains infected. There are not many mothers and fathers who would continue to carry infection or permit other members of their families to do so if they realized what it means to the life and health of the other members of their families. If the writer, knowing what he does about malaria, should live in a malarious community and neglect to disinfect himself or any member of his family who might be infected, he would feel a great sense of remorse if another should become infected and perhaps die as a result. If public health workers who are endeavoring to control malaria would make more use of this idea of the greater probability of transmission in the family of the patient himself than elsewhere, it would be found to be a strong argument in support of the thorough disinfection of individuals.

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CHAPTER XX

SAND-FLY FEVER

BY EDGAR ERSKINE HUME, M.A., M.D., LL.D., Dr.P.H., D.T.M.

Synonyms.—Pappataci fever, Phlebotomus fever, three-day fever, summer influenza, summer fever, Mediterranean dengue, Macedonian fever, Skoplje fever. It is of interest to note that the Arabic name for the disease "Yokos wa yuskut" picturesquely means "to bite and say nothing," referring to the almost painless bite of the sand-fly. The Italian term "Pappataci" has somewhat the same significance.

Definition.—An acute tropical and subtropical fever characterized by an acute onset, a sudden rise of fever with duration of three days, fall by lysis, practically no mortality, and transmitted by the bites of several species of Phlebotomus.

Etiology.—**VIRUS.**—The disease is produced by a filterable virus which has not yet been isolated. The causative agent is present in the blood during the early stages of the disease, the patients being infective during the first day but not later. This was demonstrated conclusively by Doerr and Birt. Sand-flies which had been permitted to bite persons suffering from the disease were transported to Vienna and Netley respectively, where the genus is unknown. The insects were then made to bite fresh subjects with the result that a number of such individuals developed the disease. These experimental infections were produced provided that the sand-fly had first bitten the fever-stricken patient within 24 hours after the onset of the disease, and then only if seven days had elapsed between the two stages of the experiment. Thus, it seems that the virus undergoes some cycle in the body of the vector. Blood taken from sand-fly fever patients may be kept *in vitro* for several days and still retain its infective property, even after having been passed through a Chamberland filter.

TRANSMISSION.—The disease is transmitted by the bite of various species of the sand-fly or Phlebotomus, the most common being *Phlebotomus pappatasi* and *Phlebotomus minutus*, though many other species have been described. The female only is the blood sucker. The virus is transmitted from parent insects to their offspring or by the young eating the excreta or the dead bodies of their parents and others. It has been abundantly proven since the experiments of Doerr and Birt that if sand-flies are absent from a locality, the disease is also absent. Patients often claim that there are no sand-flies where they live but a careful search during the day nearly always reveals them. In houses they are to be found in dark places near the cornice or behind hangings. The insects are of such small size that they readily pass through the ordinary mosquito netting and so escape in the morning. The bite is not painful and frequently does not awaken the sleeper.

LIFE HISTORY OF THE PHLEBOTOMUS.—The female deposits her eggs, 40 to 50 in number, in dark, rather damp places where organic matter is

available as food for the larvæ. The eggs are laid separately and not in masses, and Newstead's observations tend to show that complete oviposition may require several days for completion and that the females may die before producing their full complement. The eggs are 0.1 to 0.15 millimeter long, elongate oval in form and thinly covered with a viscous substance. They become yellowish-brown in a few hours after deposition,

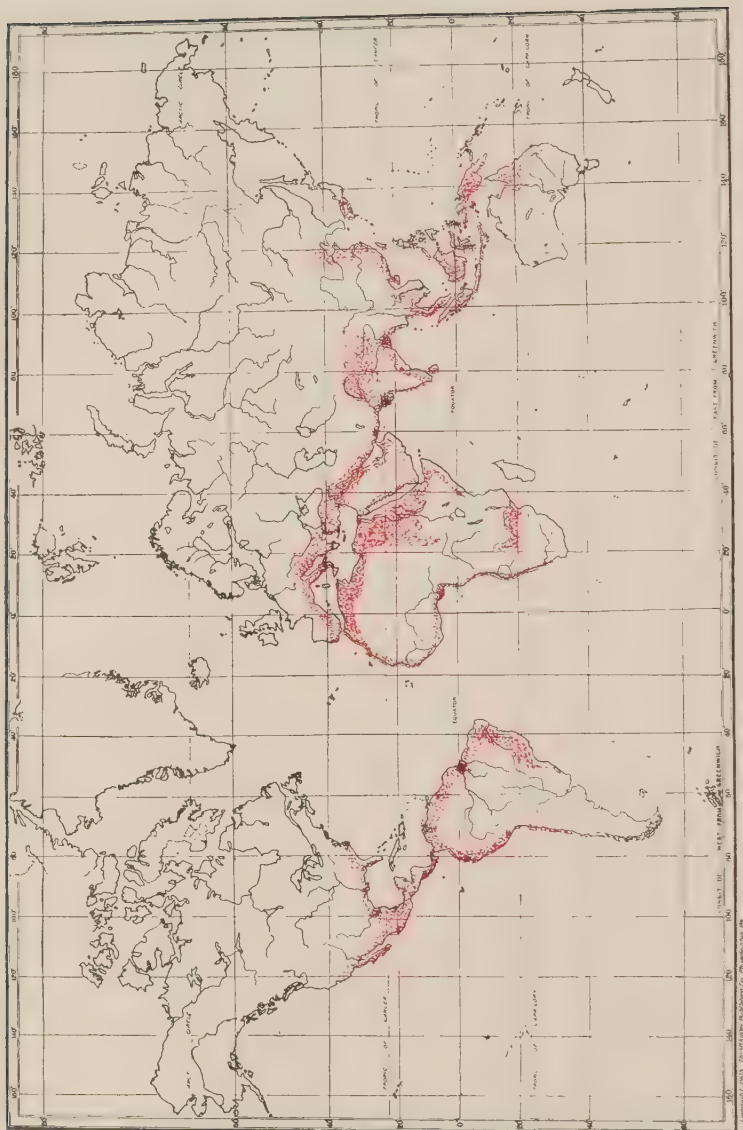


Phlebotomus papatasi

PHLEBOTOMUS PAPATASSI. Adults measure from 3 to 5 mm. in length. The position of the wings is characteristic.

the surface being coarsely reticulated. The adults bite both warm- and cold-blooded animals. Engorgement is rapid and great and in from 36 to 40 hours digestion is complete. The blood is probably an important factor in the production of fertile eggs and a meal is apparently necessary for fertilization. The food of the male *Phlebotomus* is somewhat uncertain. The length of life of the adult is unknown, though Wenyon succeeded in keeping one female alive for 48 days. They may be transmitted for considerable distances in ships and are undoubtedly distributed by coasting vessels which may account in part for the geographical distribution. Temperature and atmospheric humidity are the chief factors regulating breeding and development. Marrett states that the requisite temperature for active breeding is from 70° to 86° F. (21.1° to 30° C.) and that below 60° F. (15.6° C.) the larvæ become dormant. The conditions necessary for favorable development and the determining factors in the selection of breeding places are (1) the presence of moisture in moderate degree, (2) the absence of light and (3) the presence of nitrogenous organic matter.

OCCURRENCE.—Sand-fly fever occurs during the hot months of the year, a mean temperature of 70° F. (21.1° C.) being necessary for its



THE DISTRIBUTION OF SAND-FLY FEVER

development. Below this temperature the sand fly cannot go through its proper cycle. From the accompanying map of the geographical distribution of the disease, it will be seen that it is found in all parts of the world, depending only on the prevalence of the necessary temperature. The altitude is important as in localities high above the sea level where the temperature is low the disease does not occur. Lower down on the same mountains or plateaux the disease may be found.

It has been noted that the disease is apt to attach itself to certain buildings and from the fact that persons sleeping in the lower stories are more likely to become infected, it would seem that the insects do not fly high as a rule. A more probable explanation may be that if unprotected individuals are to be found on the lower floors there is no necessity for the sand-flies to go higher in search of blood. The flies live and breed in old walls, cracks and fissures of buildings, in caves, in sand cracks on the ground, etc., a certain amount of moisture as well as darkness being necessary for their development. The larvae feed on the excretion of bats, lizards and the like, and the adult fly has been seen to feed on these animals. It is usually stated that the sand-fly does not travel far from its breeding place and observation by medical officers of the allied troops in Macedonia, during the Great War, seem to bear out this statement. Some sanitarians go so far as to claim that a building situated more than fifty yards from the breeding places of the fly is relatively immune. The insects cannot withstand any considerable current of air and hence bite chiefly on still nights.

While sand fly fever is usually an endemic disease, it may at times attain epidemic prevalence. Epidemics vary in severity not only from time to time but from place to place.

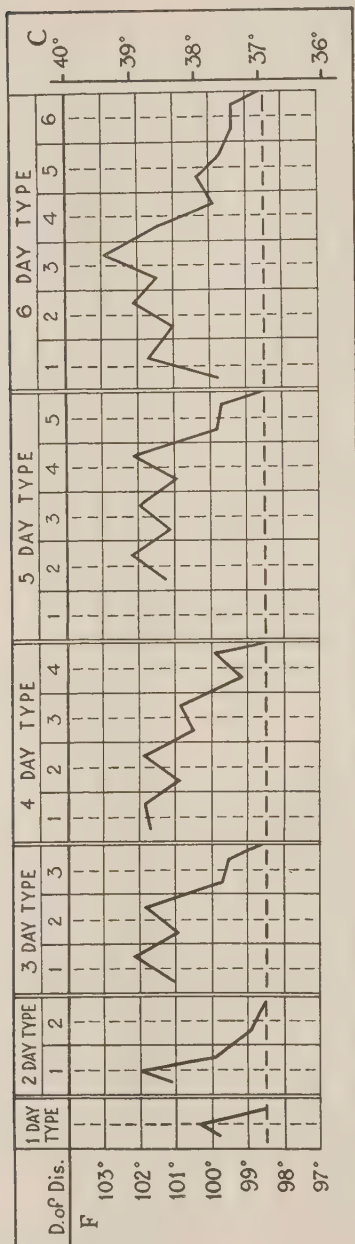
Symptomatology.—**INCUBATION PERIOD.**—The usual incubation period is from three to seven days. Experimentally the disease has been induced to occur in as short a time as 16 hours, while the longest period is about nine days.

Prodromal symptoms are usually so slight as to cause the patient little or no inconvenience, though in some cases there are muscle pains, loss of appetite and lassitude.

Onset is sudden, beginning with a slight feeling of chilliness or more rarely rigor and intense frontal headache. The temperature rises rapidly to 102° or 104° F. (39.4° or 40° C.). The character of the headache is important. It is frontal and usually postorbital, the patient complaining that his eyes feel as though they would start from his head. The eyes are quite tender to pressure and there is marked injection of the conjunctiva. Photophobia usually exists. At times the injection of the eye may be so marked as to remind one of an infection by the *Hemophilus* (*Bacillus*) of *Eye Weck*. The lids are partly closed and if drawn apart the injection will usually be found to extend in a horizontal band across the eyeball rather than covering the whole.

The face and neck are flushed, the redness often being almost a rash. *Carroll* has described a peculiar feature of this erythema, viz. it persists for 10 to 15 days after the fever has subsided and fades away very slowly. Thus it is often easy to recognize persons, especially blondes, who have recently recovered from the disease.

The patient may complain of general muscle pains of exacerbating character, particularly in the calves and loins. All motion is painful



TEMPERATURE CHARTS ILLUSTRATING TYPES OF SAND-FLY FEVER.

Modified from Birt (J. of R. A. M. C. for March 1910). The graphs are constructed from the mean of many charts.

so that the sufferer is perfectly willing to lie quietly in bed. He is apt to be irritable and to complain at any sounds. Though insomnia may occur, the individual is more likely to be drowsy and even unable to walk on account of the vertigo.

The gastro-intestinal system is disordered. There are severe attacks of vomiting, especially at the beginning of the disease, and persistent constipation. While the vomiting lasts there is marked loss of appetite, the patient in some cases declining food altogether. More rarely there may be attacks of diarrhea with hemorrhage from the bowel. The tongue is heavily coated on the dorsum with white or brown material, but the edges are clean. The liver and spleen are not enlarged, an important diagnostic point.

The throat and palate are usually congested, injected and irritable. The gums and buccal mucosa bleed easily. There may be small hyperemic red spots on the palatal mucosa, but these do not extend to the hard palate.

The blood picture is an early leukopenia which persists well into convalescence, averaging 3,000 leucocytes per c.mm. There is a relative diminution of polymorphonuclear leukocytes and an increase in the large mononuclears. The following may be regarded as a typical blood count:

Polymorphonuclears	61.1 per cent.
Lymphocytes	21.4 per cent.
Large mononuclears	14.2 per cent.
Eosinophils	2.8 per cent.
Transitionals	1.5 per cent.

The urine is of a febrile character but usually clear, acid in reaction and not very highly colored. There is usually no albumin, or if any, only a trace.

On the third day, the temperature falls to normal or subnormal, but there is sometimes a terminal rise. Accompanying the reduction in temperature there is often epistaxis and profuse sweating, a sharp contrast to the dry skin noted in the course of the disease. The heart rate is slowed during the illness. With the return to normal temperature the symptoms usually abate but convalescence is sometimes greatly prolonged. For one to three weeks the patient is debilitated and unable to perform his duties. In this characteristic of the disease lies its economic seriousness to the community.

Diagnosis.—The important points to be borne in mind are the season of the year, the presence of phlebotomi in the locality, the sudden onset, the flushed face and neck, the band-like injection of the conjunctivæ, the pains in the eyes and muscles, the leukopenia, the absence of rash and the rapid rise of fever ending on the third day. An examination of the skin, particularly the wrists and ankles, will usually reveal the sand-fly bites as red punctures often appearing papular.

The disease most likely to be confused with sand-fly fever is dengue and most of those who have had that experience with the two maladies assert that it is impossible to differentiate sand-fly fever from the mild cases of dengue. Dengue is more epidemic in character, the pains are more in the bones and joints, there is a characteristic rash and the fever instead of ending on the third day usually recurs after an afebrile period of a few days. In both diseases there are hemorrhages from the mucosæ and leukopenia.

Influenza, which resembles sand-fly fever in many ways, is a winter disease; the blood picture is different and the catarrhal symptoms are more pronounced.

Malaria may be diagnosed by the presence of the parasites in the blood, the temperature chart and the enlargement of the spleen. Phillips stresses the complaint of the malaria patient that he has "fever" while the sand-fly fever patient complains of "pains."

Mild attacks of yellow fever with their pains, leukopenia with relative increase of mononuclears and tendency to hemorrhage, may be difficult to differentiate, especially where both diseases are endemic. More severe cases of yellow fever, of course, offer no difficulty.

The diseases of the typhoid-paratyphoid group begin more gradually and are of longer course and we have the assistance of the laboratory in making the blood culture or later the Widal test.

In localities where typhus fever and sand-fly fever are coexistent the diagnosis may offer great difficulty, but the leukocytosis of the onset of typhus affords valuable assistance. The differences in seasonal occurrence are of course significant.

Treatment.—**PROPHYLAXIS.**—The only way to escape the disease in endemic districts is to avoid the bite of the insect. Attempts should be made to protect both the well individual and the patient from the sand-flies. The *Phlebotomus* being smaller than the mosquito, the ordinary mosquito net or screen is of no value. Sand-fly nets are manufactured and have meshes so small (40 to 45 to the inch) that the sand-flies cannot pass through. These, however, keep out so much air that their use is attended by great discomfort, so that in the tropics or during very hot weather in the more temperate zones, they are of but little practical value. Camphor and kerosene seem, when placed inside the mosquito netting, to have some value in driving away the insects. Attempts have been made to spray the outside of the mosquito nets with a solution of naphthalene or formalin which have a distinct value in keeping away the insects, but are very unpleasant for the sleeper. Punkahs and electric fans are useful in keeping away the flies, and the removal of bedrooms to the upper stories of buildings is not without its use.

In addition to screening with its disadvantages, the following measures are among those recommended by the Royal Air Force Sand-fly Fever Commission:

(a) Free ventilation and artificial air currents. When electric fans or punkahs are employed, they should be directed against the open window.

(b) The admittance to the rooms of as much light as possible during the day, the use of powerful electric lamps if practicable until dusk, succeeded by the employment of fans at the windows.

(c) Reduction of hiding places. The walls to be rendered as free as possible from hangings, pictures and other articles, the beds to be kept in the best lighted parts of the room, away from the walls. At times the felling of trees in immediate proximity to the house is desirable.

(d) Repellents. Besides camphor and kerosene, which have been mentioned, many formulæ have been suggested. These contain chiefly combinations of the oils of anise, eucalyptus and cassia together with materials to form an ointment. Tobacco smoke is an excellent repellent.

(e) Fumigation of the rooms with suitable insecticides, one of the best of which is pyrethrum.

(f) Traps. Box traps lined with dark cloths placed high up in the dark portions of the rooms. These should be examined daily and the flies killed with ammonia fumes.

(g) Destruction of the breeding of the sand-fly. This is at once the most important and the most difficult measure. Superfluous stone walls in bad repair in the neighborhoods of towns and villages should be removed. Constant supervision of the walls in the proximity of infested areas is required. All holes and crevices, even the most minute, should be filled with cement or other suitable material. Crevices in and near buildings should be watered daily. No heaps of stones, bricks, refuse material, etc., should be tolerated within a radius of 100 yards from the nearest habitation. Rough ground to be cleared of weeds and all holes disclosed to be filled with beaten earth. Gardening should be encouraged.

Certain natural enemies of the sand-fly are known. In Malta, a chelifer attacks the larvæ and the mite and a fungus attacks the adult. McKie has described in India a flagellate protozoon in the intestine of the fly.

MEDICINAL.—The treatment is purely symptomatic. No drugs of value are known other than the various antipyretics, the most satisfactory of which is **pyramidon**. **Aspirin** relieves the pain in some individuals but in others has but little effect. The disease is self-limited and during its continuance the patient should be kept at complete rest in bed and on soft diet.

Complications and Sequelæ.—These are not as a rule serious. The most important is the weakness which characterizes the period of convalescence. In more severe cases there may be bronchitis, phlebitis, or even nephritis, orchitis and parotitis. A peculiar loss of memory has been noted. While the usual period of the disease is three days, it may last for four or five. In fact, there are in the tropics a number of ill-defined fevers lasting from four to seven days or longer which may be varieties of dengue or sand-fly fever or both.

Mortality and Morbidity.—The disease is not primarily a serious one and the mortality is practically *nil*, but it is of considerable importance since it produces a great degree of prostration, though fortunately of a short duration. It has been a factor of great military importance, for the non-effective rate among troops who are not immune to the disease and who enter endemic zones is extremely high. It was stated that the occurrence of sand-fly fever among the British and French troops in Macedonia at one time enabled the Bulgarian forces, who were immune, to make a decided gain. Similarly, workmen and others taking up their occupations in areas where the disease exists may expect to become more or less incapacitated for a time unless preventive measures are taken.

Immunity.—Relapses following an attack of sand-fly fever have frequently been observed, but undoubtedly a lengthy immunity ultimately results which some believe lasts for life. It seems probable that hereditary immunity does not occur. Thus the majority of those coming to an endemic district from localities in which the disease is unknown are usually attacked during the first two years of their residence. It is

stated by Phillips that more than 90 per cent. of such individuals are attacked. From my own experience in Macedonia, I believe this figure somewhat high. Persons living in endemic zones often claim that they are immune and may even consider this immunity hereditary but it seems far more probable that whatever immunity exists among the population of infected communities is acquired from attacks early in life.

Pathology.—This is not known as the disease is not fatal.

History.—Sand-fly was first described as a fever of three days' duration occurring in the Mediterranean basin by Pym in 1804, whose observations were confirmed twelve years later by Burnett. Since that time, there have been numerous references concerning the incidence of the disease among troops from the north of Europe serving in tropical and semi-tropical countries. In 1903, McCarrison definitely differentiated the disease in Chitral when he suspected the sand-fly as the causal agent. In 1901, Doerr, Franz and Taussig published their account of the disease mentioned above. In 1915, Castellani showed that the so-called Skoplje fever of Serbia and Macedonia is really sand-fly fever. The most recent work on the etiology of the disease was done by the Sand-fly Fever Commission of the Royal Air Force. Though the disease occurs extensively in the southern part of the United States, there has been but little written about it in this country.

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CHAPTER XXI

TULARÆMIA

By EDWARD FRANCIS, B.Sc., M.D.

Definition.—Tularæmia is an infectious disease caused by *Bacterium tularensis*. Primarily it occurs in nature as a fatal bacteræmia of wild rodents, especially rabbits and hares. Secondly it is a disease of man, transmitted from rodents to man by the bite of an infected blood-sucking fly or tick, or by contamination of his hands or his conjunctival sac with portions of the internal organs or with the body fluids of infected rodents, flies or ticks. The disease was named tularæmia on account of the presence in the blood of the causative microorganism.

Geographic Distribution.—Naturally infected human cases have been reported from Washington, D. C. and from thirty-nine states of the United States extending from the Atlantic to the Pacific Coast and from the Canadian to the Mexican border. Ten states were added to the list in 1925, seven in 1926, three in 1927 and two in 1928. Although the disease has been known to exist in the ground squirrels of California since 1911, only two cases contracted in nature have been reported from that state and these had dressed wild rabbits. The disease was recognized in Japan in 1925.

Zoölogic Distribution in Nature.—(1) Ground squirrels, (2) wild rabbits and hares, (3) wild rats and (4) wild mice have been found infected in nature with *Bacterium tularensis*.

(1) The California ground squirrel, *Citellus beecheyi* (Richardson), was the animal in which McCoy discovered the disease in 1911. His original description was based on a study of thirty-two naturally infected ground squirrels. Squirrels in other parts of the United States have not been found infected except one ground squirrel found by Francis in Utah.

(2) Wild rabbits and hares. Cotton-tail rabbits (*Sylvilagus*), jack rabbits (*Lepus*) and snowshoe rabbits (*Lepus harrisi*) constitute the great reservoir of infection. Wherry and Lamb cultured *tularensis* from guinea pigs which had been inoculated from two wild cotton-tail rabbits found dead in Southern Indiana. Francis cultured *tularensis* from guinea pigs which had been inoculated with (*a*) the spleens of seventeen jack rabbits shot or found dead in Utah; (*b*) the spleen of a snowshoe rabbit found sick in Montana, and (*c*) the livers of ten cotton-tail rabbits bought in the Washington, D. C. market. Numerous observers have reported sick and dead rabbits in communities where human cases of tularæmia were occurring. Numerous cases of tularæmia have been reported in persons who had dressed wild rabbits only a very few days previous to illness.

Ohara in 1925 reported a fatal disease of wild rabbits in Japan. The heart of a rabbit found dead was used by him to inoculate a volunteer human subject, who contracted tularæmia.

Domestic rabbits raised in rabbitries and sold for food or for laboratory purposes or by rabbit fanciers have never been found naturally infected, although highly susceptible by inoculation in the laboratory.

(3) Wild rats. Dieter and Rhodes, in 1925, while engaged in the routine examination of rats for plague in Los Angeles, California, cultured three strains of *Bacterium tularensis* from guinea pigs into which they had inoculated the tissues of wild rats which had been trapped in the city of Los Angeles. This is the only record of having found the infection in wild rats.

(4) Wild mice. Perry, in September, 1927, isolated *Bacterium tularense* by guinea pig inoculation from two wild meadow mice in Contra Costa County, California, where large numbers of sick and dead mice had been observed. This is the only record of having found the infection in wild mice.

Transmission to Man.—Transmission of tularæmia to man occurs (1) by the bite of the horsefly (*Chrysops discalis*); (2) by the bite of the wood tick (*Dermacentor andersoni*, Stiles); (3) by the bite of a tick (probably *Dermacentor variabilis*) in Southern United States; (4) by contamination of his hands or his conjunctival sac with portions of the internal organs or with body fluids of infected rabbits, flies or ticks, and (5) by the bites of animals.

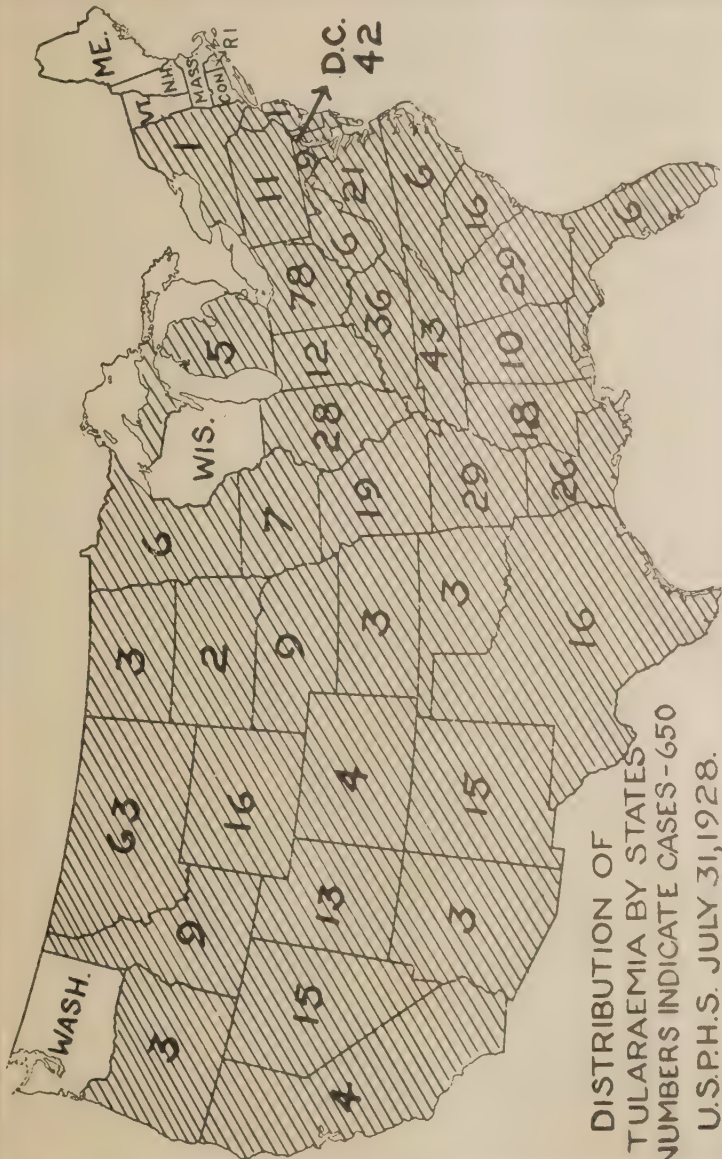
One case in Montana followed the bite of a coyote (*Canis lestes*); another case in the same state followed the bite of a ground squirrel (*Citellus Richardsoni*); a case in Iowa followed the bite of a hog (*Sus scrofa domestica*); a case in Baltimore followed the scratch of a cat; one case had killed and skinned a woodchuck. Presumably the mouth parts of the coyote, ground squirrel and hog were contaminated by infected rabbits which they had eaten because dead rabbits were found nearby, readily accessible. There is no report of transmission from ground squirrels, mice or rats to man. The only record of the transfer of infection from man to man is in a case report by Harris in which a mother is believed to have contracted tularæmia through a prick of her thumb derived while dressing the ulcer on her fly-bitten son.

1.—Flies of the species *Chrysops discalis* (Williston) are blood-sucking flies commonly found on horses and cattle, but they also bite rabbits and man. Having fed on an infected rabbit, they readily infect man at the next feed, presumably transmitting the infection mechanically by their contaminated mouth parts. These flies are found principally in Utah and the adjacent states.

2.—Wood ticks of the species *Dermacentor andersoni* (Stiles) not only transmit the infection from rabbits to man, but because of hereditary transmission of infection through their eggs to the next generation, these ticks must be considered as a permanent reservoir of infection. There is a wide distribution of infection throughout their bodies—in the lumen of the gut, in the cells of the gut wall, in their circulatory fluid, and in their faeces; they carry the infection over winter; they harbor the infection throughout their lives. They are ideal transmitters of infection. These ticks are found principally in Montana and the adjacent states.

3.—Tick bite (probably *Dermacentor variabilis*) has caused 24 cases in Arkansas, Oklahoma, Texas, Louisiana and Tennessee.

4.—Contamination or self-inoculation has caused most of the human cases. The specific acts by which man inoculates himself are the following: A market man skins and dresses rabbits for his patrons; a housewife, servant or cook dresses rabbits for the table; a hunter dresses rabbits at the end of a day's hunt; a farmer pulls infected ticks from his horse or cow and then touches his eyes; jack rabbits are skinned and cut up for fish bait, coyote bait, fox feed, chicken feed, hog feed, dog feed, for the table and for the market; persons who have become infected in the laboratory have either performed, or assisted at, necropsies of infected guinea pigs, rabbits or white mice, or have held infected living rabbits or guinea pigs, or have handled infected living ticks.



Transmission Among Wild Rabbits.—Bloodsucking insects—lice, flies and ticks—are believed to transmit the infection from rabbit to rabbit in nature, thus contributing to the maintenance of infection throughout all months of the year, and perennially.

SEASONAL INCIDENCE.—(1) Ticks and (2) flies have a seasonal prevalence, and (3) rabbits are protected by law in certain months, all of which contributes to the seasonal incidence of human cases. In every month of the year naturally infected human cases have occurred. Laboratory infections of man are without seasonal incidence.

(1) *Ticks.*—March to August are the months recorded for the onset of 33 cases of tularæmia due to tick bite in northwestern United States. These months correspond with the season of greatest activity of the tick *Dermacentor andersoni*.

February to October has marked the time of onset of 21 cases due to tick bite in southern United States. These months correspond with the season of activity of the tick *Dermacentor variabilis* which is provisionally held responsible for these southern cases.

(2) *Flies.*—June, July, August and September are the months recorded for the onset of cases due to fly bites; these months correspond to the season of greatest activity of *Chrysops discalis*.

(3) *Rabbits.*—In November, December and January it is generally permitted to hunt cotton-tail rabbits east of the Mississippi River and these rabbits are then offered for sale in large numbers in the markets; consequently, human cases east of the Mississippi River have occurred in greatest number in the months enumerated.

OCCUPATION, SEX, AGE, COLOR.—Farmers and their families furnish the largest number of cases because their occupation exposes them to ticks, flies and wild rabbits. Market men, market women, housewives and cooks furnish the second largest group of cases. Hunters and laboratory workers constitute large groups. Single cases have occurred in several professions and occupations. There were 440 males and 174 females. The oldest was 73 years of age, and the youngest was 2 years. In a series of 679 cases only 38 were negroes.

Bacteriology.—*Bacterium tulareense* is a small, pleomorphic organism, gram-negative, non-motile and non-spore-bearing; it grows only under aerobic conditions; its optimum temperature is 37° C.; its optimum pH range is between 6.8 and 7.3; it ferments glucose, levulose, mannose and glycerol, forming acid but not gas; it grows well on coagulated egg yolk and blood glucose cystine agar, but not on ordinary laboratory mediums such as plain agar, plain bouillon, gelatin, potato and milk. Additional efficient mediums are serum glucose agar, glucose blood agar, and blood agar, each having been enriched by rubbing over its surface a piece of fresh, sterile rabbit spleen which is allowed to remain on the medium. In cover-glass preparations from cultures and tissues the organism stains with ordinary dyes, but preferably with aniline gentian violet or crystal violet. In sections of tissues it stains well with Mallory's eosin and methylene blue, and with Giemsa's solution, preferably the latter. Sterile Berkefeld filtrates of virulent cultures are non-toxic to guinea pigs; in 3 of 8 attempts they passed through Berkefeld filters which held back a small staphylococcus. There is cross-agglutination between *tulareense*, *abortus* and *melitensis*.

MORPHOLOGY.—Bacillary and coccoidal forms are always seen in a young culture, but as the culture grows older there is a decrease in the

number of bacillary forms and an increase in the number of coccoidal forms until finally all are coccoidal. When an old culture is transferred to fresh culture medium, the coccoidal forms germinate into bacillary forms. Bipolar forms are seen in liquid culture medium.

Heat.—56° to 58° C. kills the organisms in cultures and in the spleen tissue in ten minutes. Cooking renders infected tissue harmless.

Formalin.—Cultures suspended in saline solution containing 0.1 per cent. of formalin (37 per cent. strength) are rendered non-virulent after 24 hours.

Trikresol.—Spleen tissue, rubbed up in 1 per cent. trikresol, was free from infection after 2 minutes.

Drying.—Two lots of infected bedbug faeces dried at room temperature on filter paper caused death of guinea pigs from tularemia when injected subcutaneously after 20 and 25 days, respectively, of drying.

BACTEREMIA.—The isolation of cultures from the blood of man during the first week of illness indicates that in man there is a bacteremia early in the disease.

Rabbits, guinea pigs and white mice dying acutely from the infection often manifest a bacteremia so great that 0.000,000,01 c.c. of their heart blood, when injected into a fresh animal, kills acutely with typical lesions of the disease.

The cœlomic fluid of the tick and the bedbug is rich in microorganisms.

SOURCES OF HUMAN INFECTION.—(1) Ulcero-glandular type—455 cases. 23 were fly-bitten (*Chrysops discalis*); 33 were tick-bitten (*Dermacentor andersoni*); 21 were tick-bitten (*Dermacentor variabilis*?); 6 were exposed to ticks, working with sheep; 4 were bitten by insects (species?); 101 were market men who had dressed rabbits; 25 had dressed rabbits bought in the market; 98 had dressed rabbits which they had shot; 34 had dissected jack rabbits; 131 had dressed rabbits the source of which was not stated; 1 had killed and skinned a woodchuck; 1 was bitten by a coyote; 1 was bitten by a ground squirrel; 1 was bitten by a hog; 1 was scratched by a cat.

(2) Oculo-glandular type—32 cases. 21 had skinned or dressed wild rabbits; 7 had crushed ticks with their fingers; 1 had handled ticks with fingers; 1 had crushed a fly with his fingers; in 2 the source of infection was uncertain.

(3) Glandular type—25 cases. 24 had dressed rabbits; 1 was an experimental human subject.

(4) Typhoid type—28 cases. 20 had autopsied laboratory animals or handled ticks; 6 had dressed wild rabbits; 1 was tick-bitten; 1 was probably tick-bitten.

NONCONTAGIOUSNESS.—No instance has been reported of the spread of the infection from man to man by mere contact or by the bite of insects which have previously bitten a patient. Surgeons who have incised or excised suppurating glands have not contracted the infection.

ABRASION AT SITE OF INFECTION.—Is an abrasion necessary at the portal of entry of the infection? This question will be discussed under two heads: (1) Presence of an antecedent abrasion and (2) Absence of an antecedent abrasion.

(1) The presence of an abrasion of the skin, either preëxistent or coincident with the time and site of infection, was recalled by only 149 of 389 cases of the ulcero-glandular type who received their infection from

dressing or dissecting wild rabbits; these abrasions consisted of cuts, punctures or scratches by fragment of shattered rabbit bone, knife, splinter of wood, iron nail, fish hook, needle, barbed wire, briar, thorn, thistle or burr. In 85 cases that were either fly-bitten, tick-bitten or bitten by coyote, ground squirrel or hog, the bite constituted the abrasion of the skin.

(2) No antecedent abrasion of the skin was recalled by 240 cases of the ulcero-glandular type who received their infection from dressing or dissecting wild rabbits. None of the 25 cases of the purely glandular type who received their infection from dressing rabbits recalled even a primary lesion of the hands. None of the 32 cases of the oculo-glandular type recalled a previous abrasion of the conjunctiva. None of the 28 cases of the typhoid type manifested even an apparent site of infection.

Turning to guinea pigs, we know that the infection will pass through the normal skin, without an abrasion and without rubbing, but causes a papule at the site of infection.

Clinical Types.—In studying 679 case reports, four clinical types are noted: (1) Ulcero-glandular, the primary lesion being a papule, later an ulcer of the skin and accompanied by enlargement of the regional lymph glands. (2) Oculo-glandular, the primary lesion being a conjunctivitis and accompanied by enlargement of the regional lymph glands. (3) Glandular, without primary lesion but with enlargement of the regional lymph glands. (4) Typhoid, without primary lesion and without glandular enlargements. Fulminant cases, running a rapid course, with death, have been noted in the first three types.

Symptoms and Course.—**INCUBATION.**—The period of incubation has been definitely determined in 259 cases in which there was a single exposure to infection; of these there was a period of 24 hours in 16 cases, 2 days in 54 cases, 3 days in 73 cases, 4 days in 58 cases, 5 days in 33 cases, 6 days in 11 cases, 7 days in 8 cases, 8 days in 1 case, 9 days in 1 case, and 10 days in 3 cases, the average being three and one-half days. In laboratory workers and market men daily exposed to infection the incubation period could not be determined.

ONSET.—The onset is sudden, often occurring while the patient is at work, and is manifested characteristically by headache, vomiting, chilliness, chills, aching bodily pains, sweating, prostration and fever.

ULCERO-GLANDULAR TYPE.—These patients complain, within 48 hours after the onset, of pain in the area of the lymph glands which drain the site of infection. On examination these glands are found to be tender and slightly enlarged; only the regional glands are involved and not those of other parts of the body. The glandular pain precedes by about 24 hours any definite reference by the patient to the site of infection, which now becomes manifest as a painful, swollen, inflamed papule which breaks down, liberating a necrotic core or plug and leaving an ulcer about three-eighths inch in diameter, with raised edges and having a punched-out appearance; on healing, the ulcer is replaced by scar tissue.

There is redness of the skin overlying the enlarged and tender lymph glands, and this redness may be continuous to the site of infection, or red streaks may be visible on an extremity. In about half of the cases the lymph glands proceed to suppuration, and after the inflammation has subsided an abscess ruptures through a soft, thin spot in the skin. In the other half of the cases the glands do not break down but remain hard, palpable and rather tender for two or three months, gradually returning

to normal. Lymph glands other than the regional glands were slightly enlarged and tender in certain cases.

Subcutaneous nodules simulating sporotrichosis were noted on the forearm and arm in 38 cases. They were distributed not only along the vessels on the anterior surface but also over the posterior surface of



FIG. 2. Tularemia. Ulcer of finger in a market man who dressed rabbits. Case J. C. D. 19 days after onset of illness. (Dr. G. T. Brown and O. B. Hunter, Washington, D. C.)

the forearm or arm and extended from the ulcer on the fingers to the enlarged axillary glands. The nodules were firm and movable, but most of them ultimately suppurated. They varied in size from that of a pea to 1 cm. in diameter, and in number they varied from two to thirty.

Weakness, loss of weight, recurring chills, sweats and prostration are

often noted during the active stage of the disease, which lasts from two to three weeks.

OCULO-GLANDULAR TYPE.—These cases follow the general description given above, but with primary localization in the conjunctival sac instead of the skin. Of 32 cases, 29 had unilateral involvement of eye and glands, 11 being right-sided and 18 being left-sided; 3 had simultaneous bilateral involvement of the eyes and glands. In the early stage the eye manifests irritation, weeping, swelling of the lids and surrounding tissues, œdema of the ocular conjunctiva, and usually a papule on the conjunctiva of the lower lid. At the same time there are swelling, tenderness and pain in some of the following lymph glands: pre-auricular, parotid,



FIG. 3. Tularæmia. Axillary bubo in a market man who dressed rabbits. Case H. F. 40 days after onset of illness. (Dr. G. T. Brown and O. B. Hunter, Washington, D. C.)

submaxillary, anterior cervical, and, in severe cases, in the axillary group. Small, discrete ulcers appear *very* soon on the conjunctivæ of both lids. The constitutional reaction is manifested by fever, chills, sweating, prostration, and, in severe cases, by convulsions, delirium and stupor. A purulent dacryocystitis was noted in three cases. In half of the cases the glands suppurated. No involvement of the sinuses was noted.

Permanent impairment of vision was noted in only one case which proceeded to blindness following a perforation of the cornea, protrusion of the iris, and fusion of the cornea and iris into a compact mass.

Fulminant cases have been recognized only once, and even in this instance the nature of the illness almost escaped recognition. The outbreak comprised four members of a family who became ill within a



FIG. 4. Tularemia. Ulcer of knee following bite of wood tick; enlarged inguinal glands. Case G. J. 70 days after onset of illness. (Medical Clinics of North America.)

24 hour period. The cases were of the oculo-glandular type, the symptoms being bilateral in the 3 who died, but unilateral in the fourth who survived. Death occurred on the sixth, eighth and ninth day of illness, respectively. The infection seemed to have been derived from wild cotton-tail rabbits which the family were in the habit of eating fre-



FIG. 5. Tularæmia. Ulcer of cheek following bite of insect (species undetermined). Enlarged cervical glands. Case A. L. 14 days after onset of illness. (Dr. W. L. Brown and C. P. Brown, El Paso, Texas.)

quently. Tularæmia was demonstrated by animal inoculation and by cultural and serologic methods in the survivor, but in the 3 who died laboratory tests were not made either before or after death, owing to the failure of the attending physician to recognize the condition.

TYPHOID TYPE—In this type, fever was the only outstanding symptom. For want of a better diagnosis, attending physicians in these

cases have inclined to the diagnosis of typhoid until compelled to give it up by reason of a negative Widal reaction and a positive agglutination of *Bacterium tularensis*. The onset and duration of the disease in this type is the same as in the glandular types.

Fever.—Fever is always present in cases of tularemia. Complete temperature records are available only for the laboratory cases, and of these charts there are 11. Viewing the 11 charts one is struck at a glance by the constancy of the sequence of initial rise, remission and secondary rise. Following the initial fever which lasts one, two or three days, there is a remission of temperature for one, two or three days; this is followed by a secondary rise to the original height, after which there is a gradual decline to normal, the whole febrile period lasting from two to three weeks.

The early remission of temperature is accompanied by a diminution of all symptoms and the patient wants to leave the hospital for his home or return to work, but symptoms return again with the secondary rise of temperature.

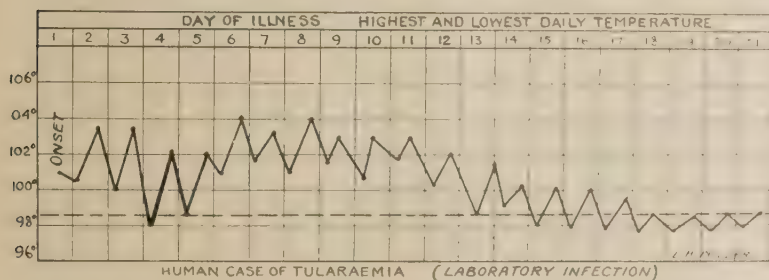


FIG. 6. Temperature Chart in Tularemia.

Leucocytosis.—The white cell count is moderately increased and may reach 16,000, but is not of diagnostic value.

Skin Eruption.—A very definite skin eruption, usually bilateral, was noted in 32 cases. It was macular, papular, pustular, maculopapular, papulo-pustular, blotchy or a rash. In some instances it was painful and inflammatory, but was usually painless and did not itch. Desquamation and pigmented remains have been noted. Many acne lesions developed on the back of the thorax during the illness in two cases. Extreme herpes of the lips was noted in one case. Jaundice was observed in one case.

CONVALESCENCE.—Convalescence is slow; it is rare for a patient to be at work again at the end of a month; usually the second month is spent lying about the house owing to weakness on exertion, and during the third month only half-time work is performed. Some have not entirely returned to normal for six months or even a year. Suppuration of lymph glands has been noted ten, fifteen, twenty-two and even twenty-four months after the onset of the disease.

RELAPSES.—Relapses of fever lasting six and eight days occurred in two laboratory cases after ten and eight months, respectively. Recurring mild attacks of fever have been noted.

Sequelæ.—Recovery usually occurs without evident sequelæ.

Complications.—Appendicitis developed on the fourth day in one case, requiring operation for removal. Ascites, accompanied by symptoms resembling a low-grade peritonitis, appeared in one case three months after onset, and *Bacterium tularensis* was isolated from the ascitic fluid. Pleurisy, with effusion into the right chest, developed four and one-half months after onset in one case.

Prognosis.—Symptoms suggesting pneumonia constitute a bad prognostic sign.

Of 679 reported cases, 24 terminated in death. Bronchopneumonia was the terminal condition in six cases, and lobar pneumonia terminated two cases. Severe meningeal involvement was indicated in six cases which manifested delirium and stupor and died in the second week, and in one which died on the sixteenth day. General peritonitis was noted in two fatal cases, in one of which there were splenic enlargement, diarrhœa, hamorrhages, and some ulcerations of the cœcum, causing death in the fifth week. A death on the eighth day was preceded by nine stools daily for four days. Coma, accompanied by albuminuria and casts, was the terminal condition in two cases which died at the end of three months and five months, respectively.

Diagnosis.—Because tularamia was not borne in mind the disease has been erroneously diagnosed as follows: (1) Clinicians have called it "flu," septic infection, typhoid fever and pneumonia. (2) Serologists have called it undulant fever on account of the cross-agglutination of *melitensis* and *abortus*. (3) Pathologists have called it tuberculosis on account of the lesions in the lymph glands. (4) Dermatologists have called it sporotrichosis on account of the subcutaneous nodules.

The clinician who bears in mind the following tetrad will seldom fail to diagnose a case of tularamia: (1) a history of having dressed or dissected a wild rabbit or of being tick-bitten or fly-bitten; (2) a primary lesion of the skin in the form of a papule, followed by a persistent ulcer or a primary conjunctivitis, followed often by ulcers of the conjunctiva; (3) persistent glandular enlargement in the region draining the primary lesion, and (4) fever of from two to three weeks' duration.

Having recognized this tetrad in his patient, the clinician will prove his diagnosis (1) by obtaining an agglutination of *Bacterium tularensis* by blood serum collected in the second week of illness and noting an increase in the agglutinin titer in serum collected a few days later or in the third week, or (2) by isolation of *Bacterium tularensis* from guinea pigs inoculated with material taken as early as the first week from the primary lesion or from the enlarged glands or the blood of the patient. Microscopic examination of cover-glass preparations and cultures taken direct from the patient is useless.

AGGLUTINATION.—A study of the blood serums of 649 cases of tularamia tested for agglutination of *Bacterium tularensis* shows (1) a complete absence of agglutinins for *tularensis* in the first week of illness; (2) the constant presence of agglutinins at some time in the second week; (3) an abrupt rise in titer in the third week, reaching its maximum in the fourth, fifth, sixth or seventh week; (4) a fall in titer in the eighth week; (5) a gradual decline thereafter until at the end of the first year the average titer of 17 cases was 1:136; (6) a persistence of agglutinins in long recovered cases, and (7) the failure of agglutinins entirely to disappear in any case, even 10, 14, 18 or 19 years after recovery.

I know of no other disease in which an agglutination test will set the diagnosis right in such certain terms after so many years. By the employment of agglutination in conjunction with other evidence in 48 cases, Simpson reported in June, 1928, a continuing record of the unrecognized existence of tularemia in Dayton, Ohio throughout the preceding twenty years.

CROSS-AGGLUTINATION.—Human tularemia sera may show cross-agglutination of *Brucella abortus* (the cause of abortion in animals) and *Brucella melitensis* (the cause of undulant fever). Of 570 human tularemia serums so tested, 129 showed cross-agglutination, while 441 failed, even in dilution of 1:10. Many of the latter group were of maximum anti-tularensis titer (1280 to 2560).

As a rule, a tularemia serum agglutinated tularensis in much higher dilution than it agglutinated *abortus* or *melitensis*, and the cross-agglutination of the latter organisms was much slower in developing in the water bath. Exceptions to that rule were noted in twelve tularemia serums which, after standing in the ice-box overnight, were found to have agglutinated *tularensis*, *abortus* and *melitensis* to the same, or to nearly the same, degree.

Human undulant fever serums may show cross-agglutination of *tularensis*. Of 93 undulant fever serums so tested, 31 showed some degree of such cross-agglutination, while 62 showed none. Among the latter group were serums which in dilution of 1:20 to 2560 gave agglutination for undulant fever.

The significance of these observations, from a viewpoint of diagnosis, is that a suspected tularemia serum should be tested, not only for agglutination of *tularensis*, but also for agglutination of either *abortus* or *melitensis* unless the clinical history points to the etiology.

ISOLATION OF CULTURE FROM MAN.—*Brucella tularensis* has been isolated directly from man by inoculation of sterile mediums by Simpson. The organism has not been identified in agar-glass preparations made direct from man. For ease of isolation human tissue is first inoculated into guinea pigs, rabbits or white mice; culture mediums are inoculated from these animals after they sicken.

ANIMAL INOCULATION.—Pus from the site of the fly bite or tick bite, or conjunctiva or from other sites of infection, or from the patient's suppurating glands, or tissue from a wild rabbit's spotted spleen or liver should be injected subcutaneously on the abdomen of guinea pigs or rabbits. Such material should first be rubbed in a mortar, suspended in salt solution, and strained through coarse gauze. Blood drawn from the patient's median basilic vein is defibrinated, mixed with an equal volume of normal saline solution, and injected intraperitoneally into guinea pigs. Each guinea pig should receive 4 to 6 cc. of the diluted blood.

Within a week the animals should die, presenting a gray, granular caseation of the enlarged lymph glands and great numbers of small white foci of necrosis studded over the enlarged spleen especially, and over the liver. The organs should be viewed in direct sunlight or in strong electric light, because the lesions are often minute; the use of a hand lens may be necessary. In the absence of apparent lesions, the death of the animal is sufficient incentive for transfer to a fresh animal.

Material from the dead animal's glands, spleen and liver, when rubbed on the shaved, abraded skin of another guinea pig or rabbit,

should likewise cause its death within a week with the same typical lesions of the lymph glands, spleen and liver, and thus the infection may be propagated for an indefinite number of passages through guinea pigs or rabbits.

Cultures of *Bacterium tularensis* may be obtained by inoculations from the blood, spleen or liver of these animals to coagulated egg yolk or blood glucose cystine agar.

More reliance should be placed on the gross pathologic evidence of the disease in guinea pigs, rabbits and mice than on cover-glass preparations made from these animals.

Spleens of infected guinea pigs or rabbits, if dropped into pure glycerol and placed in the ice-box, will remain virulent for at least a month, thus affording a means of shipping live virus for identification. Liver is inimical to the life of the infection and should not be placed in glycerin in the same container with spleen tissue.

CULTURES ISOLATED FROM MAN.—Cultures have been obtained from 24 human cases through guinea pig inoculation, as follows: (1) From blood taken during life from three patients on the 3d, 4th and 6th days of illness, respectively. From blood taken from the heart in one case on the eighth day and from a brachial vein in one case taken on the 14th day at autopsy. Blood taken during life after the first week of illness was always negative. (2) From conjunctival scrapings taken from four patients on the 4th, 13th, 13th and 17th days. (3) From pus taken from the nose on the 8th day in a case of the oculo-glandular type presenting purulent dacryocystitis. (4) From lymph glands of 9 patients taken during life on the 5th, 10th, 12th, 14th, 14th, 16th, 17th, 51st and 53d days, respectively. Numerous attempts have been made to recover the infection from the pus of lymph glands after the first month of illness, but usually the results have been negative. (5) From the primary lesion on the finger in 3 cases taken on the 5th, 8th and 17th days. (6) From ascitic fluid taken during life, three months after onset. (7) From spleen taken at autopsy on the 18th and 26th days. (8) In one additional case, cultures were obtained from the finger lesion on the 8th day, from sputum on the 12th day, and from the following tissues taken at autopsy on the 14th day: heart blood, spleen, liver and lungs.

IMMUNITY.—One attack confers immunity in man. No instance of a second attack has been recorded by practicing physicians, two of whom have observed about two hundred cases. Market men who dress rabbits year after year have had only one attack. The long persistence of agglutinins in the blood of recovered patients may be an indication of their immunity.

Susceptible laboratory animals (guinea pigs, rabbits and white mice) have exhibited no evidence of immunity to virulent infection in the author's laboratory. All died with the single exception of one rabbit which survived a severe acute attack.

SUSCEPTIBILITY.—Degrees of susceptibility are noted as follows: (1) High susceptibility in man, monkey, ground squirrel, rabbit, guinea pig, mouse, woodchuck, opossum, young coyote, pocket gopher, porcupine, chipmunk and ruffed grouse; (2) slight susceptibility in rat, cat, sheep and goat; (3) non-susceptibility in horse, cow, dog, pigeon, chicken, turkey, fox and hog.

Treatment.—**PREVENTION.**—Thorough cooking destroys the infection in a rabbit, thus rendering an infected rabbit harmless for food.

Laboratory workers engaged in performing necropsy of infected animals should **wear rubber gloves** and observe all other precautions to avoid infection. Cooks, market men and hunters should wear rubber gloves in dressing rabbits. Immune persons should be employed to dress them where possible. Infected rabbits, kept frozen for 30 days, have been found to be free from infection. The ordinary disinfectants are effective.

CURATIVE.—The treatment is symptomatic. **Rest in bed** is the most important. Those who have had the most experience with the enlarged glands **do not advise excision, or even incision**, until a very evident soft, thin place appears in the skin overlying the glands. No preventive vaccine or curative serum has yet been perfected nor has any special drug been found effective.



FIG. 7. Tularæmia. Liver of rabbit. (Collection Army Medical Museum.)

Pathology in Man.—Acute and subacute lesions are noted in man.

(1) **ACUTE LESIONS.**—Five, eight, thirteen and fourteen days after onset is the earliest that human tissue collected at autopsy has been sectioned. Lesions were found principally in the primary ulcer, lymph nodes, spleen, liver and lungs. *Bacterium tularensis* has not been stained in sections of human lesions.

Primary ulcer showed diffuse necrosis with nuclear fragmentation and infiltration with polymorphonuclear leucocytes, beneath which was infiltration with small lymphocytes.

Lymph nodes showed focal and diffuse necroses made up of leucocytes, débris and nuclear fragments.

Spleen showed on the surface, and throughout the pulp, necrotic foci containing amorphous material, nuclear fragments and a few leucocytes, and bordered by normal splenic pulp.

Liver contained small focal lesions showing necrosis of hepatic cells, the area being filled with large mononuclear cells, and, where necrosis was advanced, nuclear fragments and polymorphonuclear leucocytes were abundant.

Lung showed plaques or small necrotic foci on the pleural surface. Cut section showed small focal necroses or gray bronchopneumonic patches, or the consolidation involved almost the entire lobe. Microscopically the alveolar walls showed thickening by œdema and by large mononuclear cells, and the alveolar content was composed of a few leucocytes, red cells, and a small amount of fibrin, thus forming an alveolar pneumonia.

(2) SUBACUTE LESIONS.—Subacuteness characterizes the lesions in man after about the fourteenth day. This applies to the primary ulcer at the site of infection, the regional lymph glands which drain the site of infection, the subcutaneous nodules in the course of the lymphatics lying between the ulcer and the glands, and to the internal organs—spleen, liver, lymph nodes, lungs and suprarenals.

In microscopic sections, areas of focal necrosis are seen which show a central caseous zone surrounded by a layer of epithelioid cells and fibro-

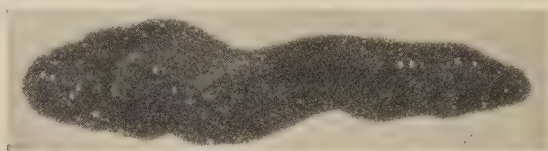


FIG. 8. Tularæmia. Spleen of rabbit. (Collection Army Medical Museum.)

blasts in radial arrangement, and a peripheral zone of lymphocytes, among which are a few giant cells. *Bacterium tularensis* has not been stained in sections of human lesions.

The granulomatous type of the subacute human lesions corresponds to the subacute clinical course, typical of the disease in man.

Pathologists, unfamiliar with the lesions in man, have tenaciously clung to the diagnosis of tuberculosis until forced to give it up by their failure to demonstrate acid-fast microorganisms or to infect guinea pigs with tuberculosis. In such cases the rabbit history and serum agglutination have proved the diagnosis of tularæmia.

Unique Features.—The following outstanding features of tularæmia deserve special mention: (1) The certainty of infection of laboratory workers. (2) The persistence of agglutinins in the blood of long-recovered cases. (3) The cross-agglutination of *abortus* and *melitensis*. (4) The granulomatous character of the lesions in man as contrasted with the lesions in animals. (5) The cystine requirement of the organism in culture medium. (6) Its pleomorphism. (7) Its penetration of the unbroken skin. (8) Its invasion of fixed tissue cells—the hepatic cells of a mouse and intestinal epithelium of tick and bedbug. (9) Its hereditary transmission through the egg of the tick to the next generation of ticks. (10) The great variety of insect hosts. (11) The great variety of animal hosts.

CHAPTER XXII

PSITTACOSIS (PARROT FEVER)

By JAMES B. LUCKIE, M.D.

Introduction, p. 679—Definition, p. 679—Etiology, p. 679—Symptomatology, p. 683—Diagnosis, p. 687—Differential diagnosis, p. 688—Complications, p. 689—Sequelae, p. 689—Treatment, p. 689—Prognosis, p. 691—Pathology, p. 691—Distribution, p. 692.

Introduction.—The study of psittacosis is not made easy like the influenza pandemic which happened when the nations of the world were organized for war. Man power was massed, and their health was under surveillance of well-equipped medical men who could command any necessary laboratory investigations. Nor is it to be compared with the investigations which marked the yellow fever campaign. In that case a great and important bit of work had to be done and yellow fever had to be conquered before this work was accomplished. It is rather an investigation of very small outbreaks in various parts of the world up to the time of the 1929-1930 epidemic, when it became a real public health problem and most of the accurate knowledge of the disease that we now have was acquired. Since then small outbreaks have occurred in Algeria, Argentina, Austria, Brazil, Canada, England, France, Germany, Scandinavian countries and many other lands, including our own, and where material has been properly handled, all of these have contributed to the sum total of our knowledge. The hope of preventing future epidemics of this disease, which may be comparable with the influenza pandemic, or similar in proportion to the tularemia outbreaks which have appeared in thirty-four states of this country, rests largely on the clinician, and he must be prepared to recognize the disease promptly.

Definition.—Psittacosis is an acute, highly infectious and contagious disease occurring in isolated and epidemic forms, and is due to a filtrable virus transmitted by birds to man. It is characterized by sudden onset of temperature, headache, exhaustion, and the rapid development of severe respiratory manifestations.

Etiology.—The predisposing causes involved in psittacosis received consideration during the 1929-1930 epidemic, which was spread over fifteen states of the United States, and temperature or climate did not seem to play a part. The outbreak occurred in the winter months in this country, except for isolated cases in spring and summer, as did also the cases in 1931 and so far in 1932; this would lead us to believe that the disease is to be anticipated at the time that we find all of the acute respiratory infections most prevalent. However, a careful study of cases throughout the world disproves this.

PREDISPOSING CAUSES.—The explanation that season seems to play such a part is probably because pet birds are so often boarded out in the summer months while their owners are traveling, and it is while in the boarding aviary or shop that they become infected, and hence are the agents for fall and winter outbreaks of the disease.

Sex.—There are many more women than men who develop the disease, and this is not likely due to any difference in susceptibility of sexes but purely to the fact that more women are coming in close contact with birds than are men.

Age.—All ages are liable although children seem to have a definite immunity. A study of cases shows the following percentages according to age.

1 to 10 years, approximately 2 per cent

10 to 20 years, 5 per cent

30 to 50 years, approximately 60 per cent

Race.—There is probably no racial immunity, but no work has been done on this subject.

Social Conditions.—The patients observed in California generally have been rather poor financially, with the exception of those working in laboratories or engaged in transporting birds. Most cases have been in people who have made a small investment in birds, hoping to earn some income from them. These birds have been handled carelessly and often housed with their owners. It can therefore be said that psittacosis has become more or less of an occupational disease.

EXCITING CAUSE.—Bacteriology.—In the same year that Eberth discovered the typhoid bacillus (1880) he also described a micrococcus which he suspected as the activating agent of psittacosis. Then in 1892, Netter suspected the Friedländer bacillus or pneumococcus. Later, Weinberg thought the disease due to a combination of streptococci and pneumococci.

In 1892, E. Nocard, working in France, aroused interest in psittacosis by finding a bacillus in the marrow of parrots' wings which was shown by him to be fatal to birds when injected. Several investigators isolated this organism in dead parrots, and Gilbert and Fournier reported finding it in the blood of a patient at autopsy, and from the parrot which had been in his care. Sicard, Eckersdorff, Bedson, Western and Simpson and several others have found it in birds not necessarily associated with human cases. This organism, they showed, belonged to the *Salmonella* or Paratyphoid group of bacteria, and was called the Nocard bacillus, or *Bacillus psittacosis*. Perry and Bainbridge reported the *Bacillus psittacosis* to be identical with *S. aertrycke*, which has a proved pathogenicity for many animals, including man, being in the latter a common cause of food poisoning. During the 1929-1930 epidemic in the United States, an intensive search was carried on by Branham, McCoy and Armstrong, of the National Institute of Health, for the Nocard bacillus in the carcasses and droppings of parrots, and in the material from human cases shipped them, but no strain of *Bacillus psittacosis* or any other member of the *Salmonella* group of bacteria was found. Their work has been

verified by careful investigators, and the Nocard bacillus is no longer generally considered the causative organism. Further work has led to the belief that a filtrable virus is to blame and this theory is concurred in by Krumwiede, McCoy and Armstrong, Rivers and Berry, and Meyer in the United States, Bedson, Western and Simpson, and Gordon in England, Elkeles in Germany, Sacquépée and Ferraboue in France and many other careful workers. The demonstration that the etiologic agent of psittacosis is a filtrable virus was quickly followed by the announcement that minute bodies could be seen in suitably stained preparations of virulent human and animal material. The observations were made independently by Levinthal (March 24, 1930), Cole (submitted manuscript April 3, 1930) and Lillie (submitted manuscript April 4th). The majority of those who have worked with the psittacosis virus (Bedson and Western, Rivers and Berry, Elkeles and Barros, Meyer and Eddie) have seen and studied these elementary rickettsia-like bodies. They appear as round or oval bodies, sometimes in pairs or clusters. The latter arrangement is particularly striking and is due to their intercellular habitat. In impression preparations or sections the reticulo-endothelial cells are sometimes filled to the bursting point with these minute bodies. Prolonged staining with Giemsa solution and differentiation with orange G, tannin solution or rapid staining with Rivers' modification of Casteneda's rickettsia stain, counter-tinged with safranin, gives excellent preparations. They are, therefore, probably related to the parasitic bodies found in spotted fever and typhus, which Doctor Roche Lima has named rickettsia bodies, and which are considered forms of the virus of that disease. When present, these L.C.L. bodies (Levinthal, Cole, Lillie), as they are called by K. F. Meyer, or rickettsia psittaci by Lillie, possess the same diagnostic value as the Negri bodies in rabies. At times, however, it is difficult, if not impossible, to demonstrate these bodies in virulent material. This difficulty is particularly striking in material from human and animal sources. However, this inability to demonstrate these bodies in virulent material with regularity is no sound reason for thinking that they are not the virus. According to Lillie, an etiologic relationship of the elementary bodies to psittacosis is indicated but not definitely proved. More recently, Bedson conducted careful filter and centrifuge experiments and found that the psittacosis virus can be thrown down almost completely by centrifugalization at a speed of about 5000 r.p.m. The particulate matter in deposit consists of minute bodies similar to the L.C.L. bodies. These elementary bodies are agglutinated by an anti-psittacosis serum and fix complement in its presence. The conclusion is therefore warranted that the minute bodies are the psittacosis virus.

MODES OF CONVEYANCE.—The infection may be direct or indirect. The disease is generally transmitted to man by birds, but man-to-man infections are known. The name would indicate that it is the parrot family only which is to blame. This is unfortunate as it will be shown that practically any of our cage birds or birds raised in aviculture are subject to infection and can give the disease, although the psittacine family is more likely to become infected by exposure and by injection of the

virus experimentally. Rice birds and even chickens are subject to the disease by injection. The parrot may or may not be the original source of the virus—that we do not know—but if so, the virus has since been scattered quite generally and many species of birds have been contaminated. By this time it probably has appeared in an unsuspected form in the majority of aviaries throughout the country and, therefore, is likely to become manifest at any time and in any place. The source of infection of any aviary is practically impossible to trace.

Birds that have so far been involved in outbreaks are: South and Central American, Brazilian, African and Indian parrots, Budgerigars, love birds, canaries, thrushes, cardinals and finches.

The virus has been demonstrated in the feces and in material from the nose, mouth and procrop of infected birds. This material when passed or evulsed dries on the cages, nests or soil of the cage and becomes pulverized. The virus is not destroyed by drying; therefore, it is easy to understand how the material, scattered by agitation or fluttering wings, can infect by inhalation. It is a common trick for birds to kiss their owners or peek at the food on their plates or even on their lips, and doubtless human cases have been contracted in this dirty manner.

The bird can infect the human during the incubation time of the disease, as is illustrated by a case where the bird was bought on December 12th, was taken sick December 21st and died December 22nd. His owner was taken sick on December 25th.

It is not necessary for a bird to show signs of sickness, although on laboratory examination the virus may be demonstrated in the spleen and liver. It is likely that some of these "carrier" birds have survived an infection contracted early in life and developed immunity by receiving minute doses of the virus over a long period of time.

Rivers' work in experimental psittacosis indicates that birds and animals that have recovered from a primary infection are refractory to reinfection. We do not know if the immunity is "sterile" or merely a carrier immunity.

McCoy states that between January and March, 1930, eleven cases developed in the Hygienic Laboratory, representing about 20 per cent of the persons employed in the building, while no cases developed in adjoining buildings. Some of these were exposed only so far as handling cultures of third and fourth generations of organisms obtained from birds, and none of these cultures were regarded as causative of the disease in bird or man. Eight others in the laboratory building who were victims of the disease had nothing to do with the work on psittacosis, but were merely working in the building as cleaners, nightwatchman, etc., and had never been in the rooms where the birds were kept or examined. No good grounds could be established for their infection.

The bite of an infected bird has been traced as the cause of infection in a few cases.

Badger, in his report of sickness in twenty-five employees in a department store which sold birds, gave histories typical of psittacosis in

17 of them, and parrots in other sections of the country that had been obtained from the same source had caused psittacosis.

The disease is highly communicable from bird to man, while instances of infection from man to man are supposedly rare, but the writer has had two cases of such transmission in the day and night nurses of his first psittacosis patient. They did not approach the birds, which were in the back yard, and one wore a mask all of the time while on duty, yet one developed the typical disease in two weeks and one in sixteen days. These two, however, may come under the head of "Contaminated Environments."

The following list is a record of other known human case-to-case transmissions:

- 1898 nurse (Leichtenstern)
- 1929 (fatal) 1 physician and 2 nurses (Potsdam)
- (fatal) practical nurse (Hamburg)
- 1 head nurse, 2 nurses, 1 orderly and 1 ward patient (Hamburg)
- (fatal) 1 physician, 1 nurse and orderly (Altoona)
- 1 nurse attending 2 cases
- (fatal) 1 nurse attending case for 5 days (Armstrong)
- (fatal) 1 nurse attending case for 8 days (Armstrong)
- 1 physician and sister of patient (Buchanan)
- 1930 5 persons exposed; no precautions; 3 contracted psittacosis (Hatfield)
- (fatal) nurse (Fisher and Helsby)
- 1932 2 nurses (Pasadena, California)

Symptomatology.—The incubation period of the disease is generally considered to be from 6 to 15 days after exposure, but some cases have developed after five and six weeks, and others have been reported as late as 82 days after exposure. During this period the patient may occasionally have an anxious, nervous feeling with slight headaches.

ONSET.—The symptoms which cause the patient to call for medical aid are fever and severe headache, accompanied by a tight feeling around the chest. The pulse is lower in proportion to the temperature than in any disease the author has observed. It is not uncommon to find a normal pulse rate with a temperature of 104° , and one case had a good quality pulse of 90 with a temperature of 106° on the sixth day of his illness. The pulse does not take a decided ascent except in the cases that prove fatal or in which complications develop. Figures 1, 2, 3 and 4 show the course of respiration, pulse and temperature in four distinct types of the disease. Case 1 (Fig. 1) was fatal, Case 2 (Fig. 2) severe but recovered in a comparatively short time, Case 3 (Fig. 3) severe but of long duration, in fact has never quite recovered from semi-delirium and headaches, and Case 4 (Fig. 4) quite mild and of short duration.

A study of the above illustrations will also show that respiration is only slightly affected, except in the fatal case which terminated on the fifteenth day of illness. The respiration and pulse both began rising on the ninth day. The temperature continues to show a decidedly irregular course throughout the disease. The tongue may have a grayish-brown, heavy coating accompanied by a bad taste in the mouth. Cough usually is associated with the onset, and is unproductive of sputum, or only slightly so. The small amount of sputum that is raised may be streaked

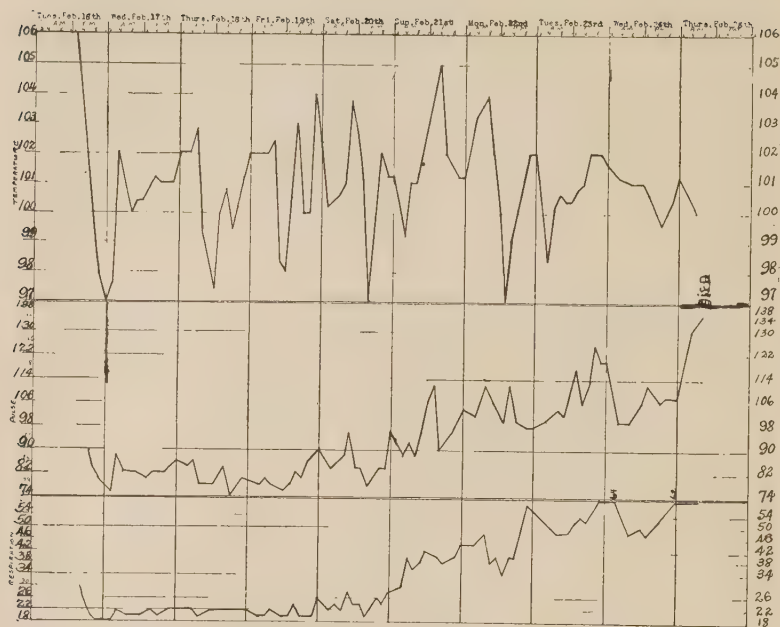


FIG. 1.—PSITTACOSIS. CASE 1.

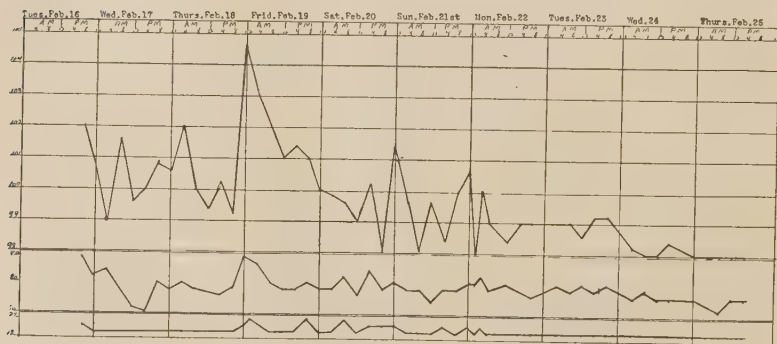


FIG. 2.—PSITTACOSIS. CASE 2.

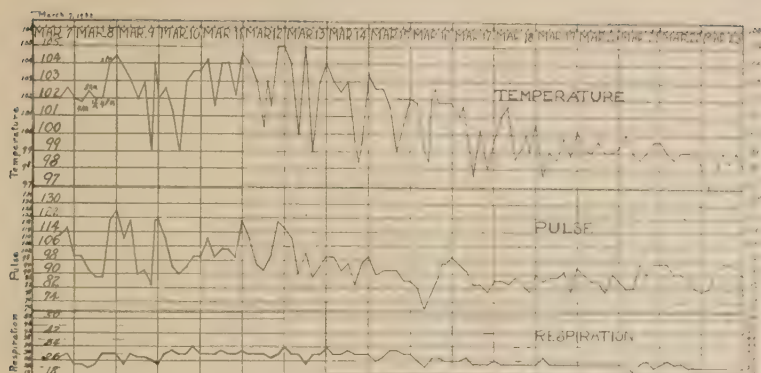


FIG. 3.—PSITTACOSIS. CASE 3.

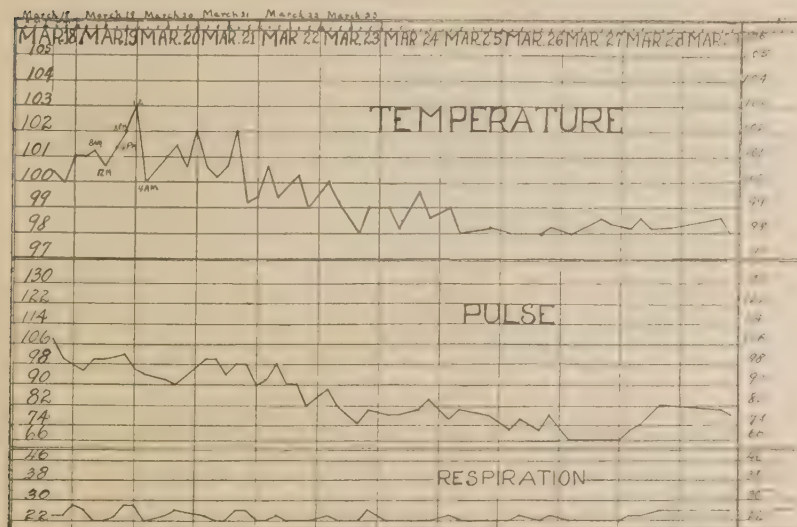


FIG. 4.—PSITTACOSIS. CASE 4.

slightly with blood, but it is not dyed with it, as in some other pulmonary diseases or ordinary pneumonia. The blood is usually due to a rupture of small blood vessels in the nose or throat, except in some very severe cases where the lungs show exudation of blood. The cough persists throughout the disease and sometimes steadily increases in severity.

The appetite suffers at first but later the patient eats very well. Diarrhea has been reported, but constipation is the general rule and may reach severe proportions.

The abdomen generally becomes distended and tender, similar to that found in typhoid the third or fourth day of illness, and remains so from

ten to fifteen days. A few rose spots may appear around the navel at the same time.

The headache becomes progressively more severe. It is first of a basilar type, later becomes general and is quite persistent, and in some cases lasts long after convalescence. In a large number of the patients, delirium manifests itself and, like the headache, may become very troublesome.

PHYSICAL FINDINGS.—The eyes are bloodshot but no conjunctivitis or discharge from the lids is found.

The nose and throat show nothing at primary examination, although previous inflammation of these parts may have existed and this must be kept in mind. Later in the disease they become distinctly reddened.

Herpes labialis may develop in the first few days, as in other febrile cases, but in the writer's experience it indicates a severe course. The case illustrated in Figure 3 showed herpes on the fourth day.

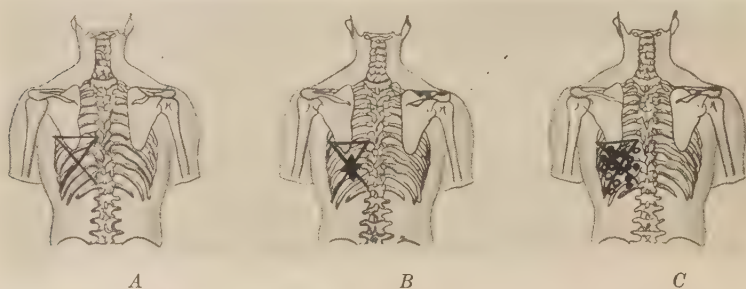


FIG. 5.—THORAX, POSTERIOR WALL—SHOWING DEVELOPMENT: A, 1ST DAY, DIMINISHED OR ABSENT RESPIRATORY SOUNDS; B, 2D DAY, SMALL PATCH DRY RÂLES; C, 3D TO 5TH DAY, DRY RÂLES SPREADING.

A papular eruption has appeared on the trunk in some cases, and may be limited to the back.

A few rose spots, similar to those in spotted fever and typhoid, are sometimes found around the navel.

The chest must be very carefully examined if the patient is seen early, for the pulmonary changes are hard to detect from the first to the third day.

At the onset the chest shows only a diminution of breath sounds without râles or dulness on percussion; this diminution as a rule is found at the left base up to the angle of the scapula, posteriorly. The author's experience has revealed only two cases out of eight with the changes in the right lung. This area should be closely watched, and on the second or third day a very small patch of dry râles may be found on auscultation about in its center. After the third day the râles spread and quickly ascend to the top of the left side. Why to the left side is not known, but the spleen probably has much to do with it. It is seldom that râles are found anteriorly, although in severe cases they may be manifest in

the right lung and be found throughout both sides. The raise of sputum is at no time abundant. There may be a small mass raised occasionally with the coughing, which is often blood-streaked but not dyed.

LABORATORY FINDINGS.—The blood picture may be practically normal, or leukocytes very slightly above, up to 13,000, or they may count as low as 4000 with a predominance of polymorphonuclears; the white cells usually drop in number steadily during the disease. There may be a shift to the left in the polymorphonuclears, and in cases showing such a distinct shift the delirium is more marked. Citrated blood taken early in the course of the disease from positive cases may reveal the virus when injected into white mice or susceptible birds such as rice birds. Agglutination tests with *Bacillus psittacosis* and other organisms were found of no diagnostic importance by Branham. Centrifugation of the blood throws down the virus, and L.C.L. bodies may be found on prolonged search in the centrifugate.

Urinalysis so far has been diagnostically valueless, giving only the findings usual in febrile conditions.

Sputum may show the usual organisms that are found with routine staining, but nothing specific for the disease, per microscope, but when injected or placed in the nose of laboratory animals it will cause the disease.

Branham also worked with the feces, but with negative diagnostic results.

No work has been done on the stomach contents.

Nasal secretions from human cases have been examined and injected into animals by Meyer, with negative results.

Diagnosis.—History of intimate contact with birds or patients ill with the disease must be obtained in all suspected cases before a diagnosis is possible (excepting laboratory workers employed where psittacosis material is handled and cases giving positive animal tests). It is not necessary, however, to determine if the birds have been sick, for it must be remembered that birds can infect during the incubation of the disease in them, and that some birds are carriers and appear perfectly well. It is important to determine if any new birds have been brought into the aviary of the sick person, or one visited by him during the preceding six months, and if any of the birds have died during that time. All cage birds should be suspected, and suspicion should not be limited to the psittacine family, for the virus is now widely spread and practically all birds raised in aviculture are susceptible.

Anxiety and slight headache precede the onset by a few days. The onset is marked by severe headache and fever from 99.6 to 104° F. The pulse is low in comparison—60 to 90. Nose bleed may come on abruptly and the mind is more or less clouded due to the exhaustion which is quite apparent. Cough may have been present for a time, and is dry and steadily progressive. Sputum is slight and blood-streaked if there has been nose bleed. In a little while all of these symptoms have increased and the headache is the chief concern of the patient.

The physical findings are scarce. The lungs show no involvement at onset other than a diminution or absence of breath sounds generally at left base, posteriorly. Later, râles appear in the sequence as illustrated in Figure 5.

Blood should be taken at once, citrated and sent to proper research laboratories, such as the Hooper Foundation, Rockefeller Institute, etc., for study and animal inoculation. This also pertains to sputum and urine when obtainable. These specimens should be repeatedly obtained, for it seems that upon certain days the blood yields negative results. According to Bedson, citrated blood tested on Budgerigars and mice contained in some cases the virus on the fourth, seventh, ninth and tenth days of illness; Berry found it to be absent on the third, sixth, seventh, eleventh and thirteenth days, and Gordon failed to detect it on the fourteenth day. The sputum has been found to carry the virus on the third, seventh and tenth days. These may, however, be just chance findings.

Virus is regularly obtained from lung, spleen and liver on post-mortem.

In order further to substantiate diagnosis in the human, the birds suspected of transmitting the infection should be chloroformed, packed in ice and immediately shipped to the same laboratory for autopsy and inoculation tests. All material should be very carefully handled and no attempts at inoculation should be made, except in the best equipped laboratories, due to the great danger of infection.

The following is a list of laboratory workers who have developed this disease by handling or coming in contact with this material:

Denmark	1 bacteriologist (Dr. M. K.)
England	1 animal caretaker 1 bacteriologist
France	9 laboratory infections at Institute Pasteur
Germany	3 veterinarians 2 physicians (1 death) 1 veterinary assistant 1 technician (died) and a man (died) living near the quarantine station
United States	1 laboratory assistant in Berlin 1 chief technician in Rostock 11 cases with one death (National Institute of Health) 2 cases, 1 fatal in Baltimore 1 case at Rockefeller Institute 1 case in a New York laboratory (1932)

DIFFERENTIAL DIAGNOSIS.—The disease must be differentiated from typhoid, typhus, Rocky Mountain spotted fever and influenza. Rivers compares it with mild yellow fever without jaundice.

Typhoid.—The history of other cases of typhoid in the vicinity must be considered, then the Widal test made. If Widal is positive, careful investigation should be made concerning the previous use of typhoid vaccine upon the patient, or the history of typhoid infection. In psittacosis the lung involvement begins almost with onset, whereas in typhoid

if pneumonia develops at all it is later in the disease. In psittacosis the typhoid-like abdomen develops around the fourth day and lasts about twelve days, and both diseases may have rose spots around the navel, but typhoid more often.

Typhus and Rocky Mountain Fever.—The bite of fleas or lice and ticks should be inquired into, as should the association with birds, for these diseases are quite similar in temperature and pulse curves. The Felix-Weil test will be of aid and other laboratory tests, as suggested by Reimann, Ulrich and Fisher, resorted to. Rickettsia bodies have been found in both typhus and Rocky Mountain spotted fever and they are probably closely related to those in psittacosis. However, pneumonia appears more often and more promptly in psittacosis than in these two infections.

Influenza.—Influenza has to be considered, but in this disease the catarrhal symptoms are more marked. The exhaustion is not so great at onset, the cough is productive of sputum, and if pneumonia develops, it is much later in the course of the disease than is the pneumonia of psittacosis. Then the story of close contact with birds, not necessarily sick birds, is quite helpful.

Complications.—Bronchopneumonia may occur at any time during the disease and cause serious complications. In a large number of patients there is a perichondrial involvement of the septum of the nose which develops late in the disease. It is possibly due to thrombosis of the delicate vessels over the septum, depriving it of circulation. In some cases this perichondritis has gone on to complete perforation of the septum. Specimens of the scrapings from such an area have been examined by K. F. Meyer, but no signs of the virus have been discovered.

Occasionally a laryngitis sicca develops and greatly disturbs the patient.

Dysmenorrhea has been seen which lasted throughout the disease.

Sequelae.—The temperature falls below normal at convalescence and is slow in rising.

Headache and inability to think clearly often persist for a considerable period after the disease.

Phlebitis of the vessels in the lower limbs may develop at any time. The writer has seen one case develop two months after the disease.

Atrophy of the legs with decided unsteadiness of gait has been seen by Rivers and the writer. This is quite persistent and more marked than is generally found in other febrile diseases.

Treatment.—**Prophylaxis** in general consists in bird owners exercising greater care in their aviaries by keeping the dust laid in and around the aviaries with one of the calcium products sold for this purpose. All loosened feathers and other débris, as far as possible, should be burned, and, above all, new birds should not be brought in from other aviaries until quite certain that the source is free from disease. If birds show signs of illness, they should be chloroformed at once and sent to a laboratory for postmortem examination. If positive, the aviary should be quarantined until proved innocent.

Kissing birds and allowing them to eat from one's dishes or from one's lips is a vicious practice and should be stopped.

Nurses and physicians should wear masks when with the patient, and rubber gloves when handling the patient or his excretions. Tissue paper for sputum and bags for the same should be burned. Feces and urine should be treated at once with cresol.

The patient should be isolated and his surroundings very quiet, for excitement tends to make the headache and delirium worse.

Diet can and should be full with the exception of stimulating and irritating foods.

The headache is the chief concern of the patient and requires more or less constant medication. The old familiar migraine formula of **phenacetin**, **acetylsalicylic acid** and **caffeine** has worked well with some cases. Narcotics may have to be used, but seldom.

Cough is the next disturbing element and is a real tax on the therapist. The usual syrups used for this purpose are failures, and **codeine** or other mild opiates have to be used. Where laryngitis is a complication the cough and the laryngitis are both benefited by **inhalations of steam** with compound tincture of benzoin added to the water.

Unless the fever attains serious proportions, the migraine mixture used for headache will take care of it nicely. Tepid baths may, however, be necessary to reduce it.

The heart must be watched and **cardiazol**, **caffeine** or **digitalis** resorted to when necessary.

There is no specific vaccine or serum for the infection. Convalescent serum has been tried by Adamy and others but showed no results that could be classed as curative or even beneficial.

The writer, feeling that a positive leukocytic response would be of benefit, used massive doses of **leukocytic extract**, prepared by the Archibald method, to excite this response. It was useless in small doses, but five cubic centimeters given hypodermically or intramuscularly every four hours, night and day, seem to influence the disease remarkably. Any vaccine, serum or other agent which irritates the reticulo-endothelial beds is worthy of a trial. English authors report results with anti-meningococcic serum and typhoid vaccine.

A mixture of quinine and camphor in vegetable oil was used intramuscularly, but without appreciable benefit to the pneumonia.

The nose may need care due to the perichondritis that sometimes develops. Use either zinc oxide ointment, in a collapsible tube with nasal tip, or yellow vaseline, and allow it to remain in the nares as long as possible. White vaseline is bleached and is liable to cause irritation if placed in the nose. An antiseptic of a mild nature, like those prepared in water-soluble jellies, can occasionally be used with benefit.

Convalescence has to be very carefully considered, as relapses are common and phlebitis is likely to develop. The patient should live quietly and without physical exertion or labor for at least thirty days after the temperature drops, if the case has been a severe one. After

this, the exercise and labor should be very gradually resumed, and even then a relapse may occur.

Although there may be leg weakness, with atrophy of the leg muscles, massage must be avoided due to the danger from thrombosed vessels.

Prognosis.—Certain factors must be considered in the prognosis of this disease and one of these is age. In the 675 cases reviewed, the age incidence was as follows:

Age susceptibility	Death rate
1 to 10—approximately 1.5 per cent	Low
10 to 20—approximately 5 per cent	Low
30 to 50—approximately 60 per cent	50 per cent
50 to 60—approximately 15 per cent	50 per cent

Although the death rate was unobtainable in the above cases under thirty years of age, the younger patients are considered as having much better chances of recovery than those above thirty years. The death rate throughout the world approximates 40 per cent for all ages—in California, 20 per cent, or 9 out of 43 cases, of which 13 were males and 30 females.

Functionally, the surviving patients ultimately become normal, but some have an atrophy of the leg muscles with weakness, while others have a clouded mentality for some time.

Pathology.—**MACROSCOPIC.**—The chief autopsy findings in cases dying of the disease are present in the lungs, which are involved by rather typical pneumonic processes, including, as a rule, more than one lobe. The involvement is definitely lobar, the diseased lobes are very large, uniformly consolidated, heavy, moderately firm, and on section are extremely moist, gray-white with a slight shade of blue in color. The sectioned surface is smooth, glassy, homogeneous, and the granular appearance of lobar pneumonia is absent. A large amount of fluid exudes on firm pressure. Some describe the lesion to appear about midway between a marked edema and a gray lobar pneumonia. There are no hemorrhages seen or any peribronchial change, as seen in influenzal pneumonia. There is some reddening of the tracheobronchial tree, and in the lumen of the bronchi fibrinous exudate is found. Occasionally a complicated bronchopneumonia may cause a purulent secretion in the bronchi and gray or reddened consolidated portions about the bronchi.

The pleural surfaces of the involved lobes are smooth and glistening and devoid of fibrinous exudate. The tracheobronchial lymph nodes show a moderate inflammatory hyperplasia.

The heart, liver and kidneys show cloudy swelling of various degrees. Occasionally fatty degeneration is found in patches in the liver, and in virulent cases small focal necroses similar to those found in infected birds or mice are present. The spleen is moderately enlarged and soft as in other severe infectious processes.

The brain and cord and their meninges in a few cases in which examination has been made have shown a diffuse hyperemia and edema. Small pin-point ring-shaped hemorrhages have been described by some. The

rest of the organs show no noteworthy findings, except complications, such as bronchopneumonia, phlebitis of lower extremities, etc., in a few cases.

MICROSCOPIC.—Sections of the involved portions of the lungs in uncomplicated cases show a characteristic picture. The alveoli are filled with an exudate of serum and various amounts of fibrin in the meshes of which are found a moderate number of large mononuclear macrophages. Polymorphonuclears as found in lobar and bronchopneumonia are absent and extremely rare. The alveolar walls are thickened, due to engorgement of the vessels and the presence of macrophages in the stroma. The bronchi and bronchioles are particularly free from change. Their lumina may contain exudate similar to that in the lung alveoli, but purulent or mucopurulent secretion as in the more common pneumonias is absent. Occasionally small arterioles are thrombosed and necrosis of surrounding alveolar walls has been found.

Smears or sections made from the lung parenchyma when stained by Giemsa or other proper technic may show L.C.L. intracellular rickettsia-like bodies in the macrophages of the exudate. As a rule a few pneumococci or streptococci or other agonal or preagonal invaders may be found in the bronchial exudate.

The liver, kidneys and heart show nonspecific parenchymatous degeneration. Small focal necrosis or patches of fatty degeneration in the liver may be found in fulminant cases. The spleen shows marked congestion and hyperplasia of the endothelial cells in the pulp. L.C.L. bodies have been found rarely in the Kupffer cells of the liver and the endothelial cells of the splenic pulp. However, the finding of these organisms in human material is more difficult and success is much less often encountered than in mice or birds.

Distribution.—The following chart will give a general idea of the distribution of psittacosis throughout the world.

Distribution of Psittacosis
1929-1932

(Approximately 675 cases; Mortality 35 to 40 per cent)

	1929-1930	1931-1932
Algeria	9 cases	
Argentina	Approximately 100 cases	
Austria	7 cases	
Brazil	Few cases in Rio de Janeiro and Porto Alegre	
Canada	7 cases	
Czechoslovakia	6 cases	
Denmark	5 cases	
Egypt	1 case	
Hawaiian Islands	1 case	
England	125 cases	
Germany	215 cases	
Holland	12 cases	
Italy	5 cases	
Poland	2 cases	
Portugal	Few cases	
Spain	Few cases	
Sweden	6 cases	

Distribution of Psittacosis—*Continued*

Switzerland	44 (39 University Campus epidemic at Zurich)	
United States	169 cases	
California	10 cases	48 cases
New York City ...		7 cases
Chicago		3 cases
		(due to California birds)

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